CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210491Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 210491 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Symdeko Established/Proper Name: Tezacaftor/Ivacaftor Dosage Form: Tablets		Applicant: Vertex Pharmaceuticals Inc. Agent for Applicant (if applicable):
RPM: Jessica Lee		Division: DPARP

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 2/28/18	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Social Media
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 2/12/18
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	9/25/17; 7/10/17 9/21/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 1/25/18 DMEPA: ☐ None 1/10/18; 10/13/17 DMPP/PLT (DRISK): ☐ None 1/5/18 OPDP: ☐ None 1/5/18 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	1/25/18 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Designation	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted 1/28/14
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	1/17/14
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	1/330/18; 1/26/18; 1/19/18; 1/9/18; 1/5/18; 1/3/18; 12/28/17; 12/8/17; 10/30/17; 10/20/17; 10/4/17; 9/1/17; 8/23/17 (2); 8/18/17; 8/1/17; 7/10/17 **CMC:** 1/5/18; 11/21/17; 10/18/17; 10/2/17; 8/21/17; 7/28/17; 7/20/17; 7/7/17; 7/6/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	2/12/18; 1/12/18
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 5/30/17
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 11/5/14
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 11/2/17
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 12/19/17
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	5/16/17 (CMC); 9/14/16 (CMC)

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None Refer to DD Review 2/12/18
Division Director Summary Review *(indicate date for each review)*	☐ None 2/12/18
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 1/19/18
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	2/1/18; 8/4/17
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical review dated 2/1/18, pg 102
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None IRT/QT 10/10/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	 2/5/18 ☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 1/27/18; 1/16/18; 11/22/17; 11/17/17 (2)
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 2/5/18; 8/11/17

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/2/18; 8/14/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 2/2/18
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 1/31/18
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2/2/18; 1/29/18; 12/6/17; 8/7/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 1/30/18; 11/22/17
❖ ECAC/CAC report/memo of meeting	☐ None 11/21/17 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 1/29/18; 7/25/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC review dated 1/29/18
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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/s/

JESSICA K LEE
02/13/2018

Rare Pediatric Disease Priority Review Voucher eligibility checklist

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher. An application that does not meet all of these criteria is not eligible for a voucher.**

NDA 210491	**Review Division DPARP**
Requirement	**Meets? (yes/no)**
For prevention or treatment of a *rare pediatric disease? (OOPD/OPT makes determination)*	Yes – 12/20/2017 (determination was made during the review)
Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act or section 351(a) or 351(k) of the PHS Act?	Yes – NME in DARRTS
FDA deems eligible for priority review?	Yes
Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act?	Yes (filing meeting 8/4/2017)
Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population?	No. The application did not rely on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population. See section 529(a)(4)(D) of the Federal Food, Drug & Cosmetic Act (21 U.S.C. § 360ff(a)(4)(D)). This application, and this approval, instead relied on clinical data derived from studies that examined an adult population, albeit with the inclusion of some pediatric subjects age 12 and above.

Does not seek approval for a different adult indication in the original rare pediatric disease product application?	Yes per draft label

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/s/

ALTHEA CUFF
02/12/2018

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comments:

> Find attached the revised version of the label. In addition to the revisions in the label, update the dates in the label to February 2018. Submit a clean and track changed version of the label incorporating our recommended changes to the NDA by February 2, 2018. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label continues to be reviewed.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: SChin 1/30/18
JLee 1/30/18

Initialed by: LBrodhead for LJafari 1/30/18

Finalized by: JLee 1/30/18

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/s/

JESSICA K LEE
01/30/2018

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comments:

> Find attached the revised version of the label. Submit a clean and track changed version of the label incorporating our recommended changes to the NDA by January 30, 2018. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: SChin 1/26/18
JLee 1/26/18

Initialed by: LJafari 1/26/18

Finalized by: JLee 1/26/18

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/s/

JESSICA K LEE
01/26/2018

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comments:

> Find attached the revised version of the label. Submit a clean and track changed version of the label incorporating our recommended changes to the NDA by January 24, 2018. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: ADurmowicz 1/19/18
JLee 1/19/18

Initialed by: LJafari 1/19/18

Finalized by: JLee 1/19/18

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/s/

JESSICA K LEE
01/19/2018

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comments:

> Find attached the tracked change and clean version of the Patient Information label. Submit a clean and track changed version of the label incorporating our recommended changes to the NDA by January 12, 2018. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 1/9/18
ADurmowicz 1/9/18

Initialed by: LJafari 1/9/18

Finalized by: JLee 1/9/18

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/s/

JESSICA K LEE
01/09/2018

Kinsley, Steven

From: Kinsley, Steven
Sent: Friday, January 05, 2018 12:22 PM
To: 'meghan_johnston@vrtx.com'
Cc: Aisida, Bamidele (Florence); Lee, Jessica K (ODEII/DPARP)
Subject: NDA 210491 Information Request

Dear Ms. Johnston,

My name is Steven Kinsley and I am covering for Florence Aisida who will be returning to the office next week.

Our review team for NDA 210491 has the following Information Request. Please respond to the following with a submission to your NDA by Tuesday, January 9, 2018. Also, please verify receipt of this Information Request by return e-mail.

1. It is noted that there is a potential for (b) (4) what is currently demonstrated as your proposed commercial batch size of (b) (4) kg is greater than (b) (4) the current batch size of (b) (4) kg. Typically (b) (4) what is currently demonstrated has a potential to adversely impact product quality due to factors such as (b) (4). Hence, confirm that (b) (4) will be governed by a process qualification protocol to assess the adequacy and robustness of the process, equipment, analytical systems, etc. as part of the (b) (4). Study acceptance criteria must be met prior to implementation of the larger commercial scale. The study design, protocol execution, and the assessment of the results can be managed by your internal Pharmaceutical Quality System.

2. We acknowledge the submission in Section 3.2.P.3.5 of your approach to Continued Process Verification. However, the FDA does not approve process validation protocols during an application review. The actual protocols, acceptance criteria, and study outcomes will be evaluated during an inspection of your manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov

Steven Kinsley

Digitally signed by Steven Kinsley
Date: 1/05/2018 12:26:47PM
GUID: 555cc3bc000836e194b17e8bf695ce5f

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comment and request for information:

> We note that text related to Figure 1 in Section 12.1 of the Kalydeco label states that the following mutations in the *CFTR* gene did not meet the threshold of change in CFTR mediated chloride transport of at least 10% of normal over baseline: *A46D, G85E, E92K, P205S, R334W,R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X,* and *N1303K.* Clarify if these mutations known to be negative in ivacaftor in vitro testing or any additional mutations have been assessed using the tezacaftor/ivacaftor in vitro test system and had negative results. If so, provide the results. If not, provide an explanation for your rationale not to test.

Provide your response by January 9, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: ADurmowicz 1/15/18

Initialed by: LJafari 1/5/18

Finalized by: JLee 1/5/18

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/s/

JESSICA K LEE
01/05/2018

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following requests for information:

1. Provide representative copies of the certificate of analysis for each excipient used to manufacture the (b) (4) and the final drug product. Clarify by amending the corresponding NDA sections if and how frequently you test the excipients. Also, specify quality attributes you test for each excipient.

2. Amend Section 3.2.P.7 to include technical drawings, a table summarizing individual materials of construction and their compliance to the corresponding CFR sections, and representative certificates of compliance for all immediate packaging components.

3. Revise the Post-Approval Stability Protocol and Commitment section (P3.2.P.8.2) to include the following:

    a. Provide updated stability data to the Agency in annual reports.

    b. Withdraw from the market any lots not meeting the specifications during the proposed expiration period.

    c. Report as required per 21 CFR 314.81(b)(1)(ii).

4. Revise the blister card label to place only the established names of the active inside the parenthesis. Namely, revise "(tezacaftor/ivacaftor 100 mg/150 mg and ivacaftor 150 mg tablets)" to "(tezacaftor/ivacaftor) 100 mg/150 mg and (ivacaftor) 150 mg tablets". Only the established name should be included in the parenthesis.

Provide your response by January 4, 2018. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: XShen 1/3/18
JLee 1/3/18

Initialed by: JPinto 1/3/18
LJafari 1/3/18

Finalized by: JLee 1/3/18

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/s/

JESSICA K LEE
01/03/2018

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comments:

1. Find attached the tracked change and clean (accepted) versions of the initial FDA-proposed tezacaftor/ivacaftor label edits with comments/instructions embedded in the document. As mentioned in comments within the label, additional edits, in particular to Sections 8, 12, and 13, will be forthcoming. Moving forward, in order to make continued proposals more efficient, we request you make any Vertex-proposed changes to the clean version of the label.

2. Regarding the carton and container labeling, revise the Container Blister Card Label and Carton Labeling to clarify the strength and directions to indicate that the dose is one tablet.

    a. Ensure that the established name is at least ½ the size of the proprietary name and in accordance with 21 CFR 201.10(g)(2).

    b. On the morning dose strip, revise the presentation of the established name and strength to read as follows: tezacaftor/ivacaftor 100 mg/150 mg per tablet

    c. On the evening dose strip, revise the presentation of the established name and strength to read as follows: ivacaftor 150 mg per tablet

    d. Under Instructions For Use on the blister card label and Instructions for taking Symdeko on the carton labeling:

        - Revise “Remove yellow (tezacaftor/ivacaftor) tablet by pushing through blister” to “Remove one yellow (tezacaftor/ivacaftor) tablet by pushing through blister”.

        - Revise “Remove blue (ivacaftor) tablet by pushing through blister” to “Remove one blue (ivacaftor) tablet by pushing through blister”.

Please be advised that these labeling changes are not necessarily the Agency’s final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed. Submit a clean and track changed version of the label incorporating our recommended changes to the NDA by January 9, 2018. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: ADurmowicz 12/27/17
JLee 12/28/17

Initialed by: BWheeler for LJafari 12/28/17
ADurmowicz 12/28/17

Finalized by: JLee 12/28/17

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

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/s/

JESSICA K LEE
12/28/2017

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comment and request for information:

> During review of the impurity qualification for the proposed specifications, there are some RRT listings in the Certificates of Analysis without an associated code name. Provide a table of RRTs, associated code names, and quantity detected for those compounds that have been identified for Reports VRT-893661-TX-011 (4-week dog study), VX-661-TX-012 (26-week rat study), and VX-661-TX-018 (26-week dog study).

Provide the requested information as soon as possible, but no later than December 13, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: SLeshin 12/7/17
JLee 12/8/17

Initialed by: LJafari 12/8/17
CGalvis 12/8/17

Finalized by: JLee 12/8/17

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/s/

JESSICA K LEE
12/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

MID-CYCLE COMMUNICATION

Vertex Pharmaceuticals Inc.
50 Northern Ave.
Boston, MA 02210

Attention: Charlotte Heyman, MSc
Regulatory Senior Manager, Global Regulatory Affairs

Dear Ms. Heyman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tezacaftor/ivacaftor.

We also refer to the teleconference between representatives of your firm and the FDA on November 2, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 2, 2017 at 12:00 PM

Application Number: NDA 210491
Product Name: Tezacaftor/Ivacaftor
Indication: Cystic Fibrosis
Applicant Name: Vertex Pharmaceuticals

Meeting Chair: Anthony Durmowicz, MD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Curtis Rosebraugh, MD, Director, Office of Drug Evaluation II
Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Anthony Durmowicz, MD, Clinical Team Leader, DPARP
Stacy Chin, MD, Clinical Reviewer, DPARP
Lawrence Leshin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Carol Galvis, PhD, Pharmacology/Toxicology Team Leader, DPARP
Andrew Goodwin, PhD, Supervisory Pharmacology/Toxicology, DPARP
Jianmeng Chen, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology II
Anshu Marathe, PhD, Clinical Pharmacology Team Lead, Division of Clinical Pharmacology II
Mingyu Xi, PhD, Mathematical Statistician, Division of Biometrics II
Yongman Kim, PhD, Lead Mathematical Statistician, Division of Biometrics II
James Weaver, PhD, Research Pharmacologist, Division of Applied Regulatory Science
Wendy Wu, PhD, Research Pharmacologist, Division of Applied Regulatory Science
Hobart Rogers, PharmD, PhD, Reviewer, Genomics and Targeted Therapy Group, Office of Clinical Pharmacology
Sarah Zaidi, MD, Clinical Reviewer, DPARP
Robert Lim, MD, Clinical Team Leader, DPARP
Linh Do, PharmD, Regulatory Project Manager, DPARP
Elaine Sit, PharmD, Regulatory Project Manager, DPARP
Jessica Lee, PharmD, Senior Regulatory Project Manager, DPARP

APPLICANT ATTENDEES

Nia Tatsis, Ph.D: Sr. VP Global Regulatory Affairs
Gemma Pilkington: Director, Global Regulatory Affairs
Charlotte Heyman: Sr. Manager, Global Regulatory Affairs
Reshma Kewalramani, MD: Sr. VP R&D Management
Julie Lekstrom, MD: Senior Medical Director, Clinical Development

Fred van Goor, PhD: Principal Research Fellow
Amit Sachdev: Executive VP, Chief Regulatory Officer
Jeff Chodakewitz, MD: Executive VP, Chief Medical Officer

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

The applicant, Vertex, and the Agency discussed the results from Study 109 in which (b) (4) Study 109 failed to meet the primary endpoint of demonstrating an increase in FEV1 of the tezacaftor/ivacaftor combination over ivacaftor monotherapy. The Agency conveyed to Vertex that the Study 109 results are under internal discussion and how to handle the new information and (b) (4) will need further internal discussion.

3.0 INFORMATION REQUESTS

An Information Request dated October 30, 2017 was sent to Vertex for the discussion of the methodology employed in the in vitro experiments summarized in Nonclinical Study Reports N092 and M078. Specifically, the Agency requested for explanations for the use of a triple inhibitor cocktail to suppress CFTR-mediated current in M078/N092 Study Reports (as opposed to a single inhibitor in G205 Study Report). In addition, we requested justification for the change in baseline region used to calculate total CFTR-mediated current. In M078/N092, the total CFTR current was quantified as the difference between 10 uM forskolin-stimulated current and the steady state current in the presence of triple inhibitors; in G205, the total CFTR current was quantified as the difference between the forskolin/ivacaftor-stimulated current and the pre-drug baseline value). Because the triple inhibitor cocktail always eliminated the total forskolin-stimulated current plus some (meaning that the current in the presence of tezacaftor and ivacaftor but prior to forskolin application was also reduced), the Agency was concerned with non-specificity of the triple inhibitor against endogenous non-CFTR currents and the possibility of overestimating tezacaftor/ivacaftor effects per the analysis method in M078/N092. Vertex indicated that the current prior to forskolin application but in the presence of tezacaftor and ivacaftor was in part mediated by CFTR, and that the triple

inhibitor cocktail was specific. Vertex agreed to submit additional in-vitro data to support these statements.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

No major safety concerns have been identified at this time and currently, we see no need for REMs.

5.0 ADVISORY COMMITTEE MEETING

No Advisory Committee Meeting is scheduled at this time.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Scheduled for December 19, 2017

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/s/

JESSICA K LEE
11/30/2017

From:	Aisida, Bamidele (Florence)
To:	"Meghan Johnston"
Cc:	Lee, Jessica K (ODEII/DPARP)
Subject:	INFORMATION REQUEST NDA 210491- 11/21/30
Date:	Tuesday, November 21, 2017 11:45:00 AM

Hello Meghan,

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

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

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

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

We are amenable to a teleconference to come to a consensus.

Please respond to the following with a submission to your NDA by November 30 ,2017 and confirm receipt of this email.

Thanks,
Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

Executive CAC Final Study Minutes
Date of Meeting: November 21, 2017

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ronald Wange, PhD, DMEP, Alternate Member
Timothy Robison, PhD, DPARP, Pharm Tox Team Leader
Eleni Salicru, PhD, DPARP, Presenting Reviewer

Author of Minutes: Eleni Salicru, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 210491
Drug Name: Tezacaftor (will be used in combination with ivacaftor [approved 2012]; the trade name for the combination product is Symdeko™)
Sponsor: Vertex Pharmaceuticals Inc.

Background
Tezacaftor (VX-661)/ivacaftor (VX-770) is proposed as combination therapy for the treatment of cystic fibrosis (CF) in patients 12 year of age and older who are homozygous for the F508del mutation or who have at least one mutation in the CF transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor, based on in vitro data and/or clinical evidence. Ivacaftor was approved for the treatment of CF on January 31, 2012. The carcinogenic potential of ivacaftor was reviewed under NDA 203188; ivacaftor was not tumorigenic in either 2-year rat or mouse studies.

VX-661 was negative for mutagenicity and clastogenicity in a standard battery of genetic toxicology studies (bacterial reverse mutation assay, in vitro chromosomal aberration assay, and in vivo mouse micronucleus assay).

VX-661 undergoes considerable metabolism (mainly by CYP3A4) in humans and nonclinical species. Dehydrogenation of VX-661 leads to metabolite M1 (VRT-0996107), sequential oxidation of M1 forms metabolite M2 (VRT-1189001), and phosphorylation of M1 forms M5 (VRT-1074233) (which can potentially interconvert back to M1). Metabolites M1 and M2 constitute >10% of total systemic exposure (i.e., approximately 38.8% and 35.7%, respectively) at the proposed clinical dose.

M1 is pharmacologically active with similar potency and efficacy as VX-661. The 2-year rat study achieved a greater exposure to M1 relative to the human exposure to M1 associated with the clinical dose of VX-661. Exposure to M1 was also quantified in the 26-week Tg.rasH2 mouse carcinogenicity study.

M2 is a disproportionate human metabolite (i.e., high levels in humans and low levels in rats and dogs), which is pharmacologically active but less so than VX-661. Oral administration of the M2 metabolite resulted in poor bioavailability in rats, dogs, and guinea pigs, while intravenous administration in rats resulted in deaths, and subcutaneous administration in rats was not well tolerated. Thus, it was judged that the carcinogenic potential of the M2 metabolite could not be studied. M2 was negative for potential genetic toxicity by the bacterial reverse mutation assay and the chromosomal aberration assay with human peripheral blood lymphocytes. Exposure to M2 was quantified in the 2-year rat and 26-week Tg.rasH2 mouse carcinogenicity studies and rodent to human exposure ratios were ≤0.2 with the proposed clinical dose.

M5 can potentially interconvert back to M1. M5 was detected in a human mass balance study at >10% of total systemic exposure with the proposed clinical dose, but is considered pharmacologically inactive. M5 has not been studied for potential genotoxicity. M5 was not routinely monitored in nonclinical studies with rats or dogs. The Applicant provided data that M5 is formed in rats from a single dose study, but not in repeat dose studies. It was judged that M5 was formed in sufficient levels in rats to provide an assessment of its toxic potential. Thus, it is reasonable to assume that the 2-year rat study provides an adequate assessment of the carcinogenic potential of M5.

Rat Carcinogenicity Study
In a 104-week oral (gavage) carcinogenicity study, Sprague-Dawley male rats (70 per group) received doses of 0, 5, 15, and 50 mg/kg/day VX-661 and Sprague-Dawley female rats (70 per group) received doses of 0, 5, 20, and 75 mg/kg/day VX-661. Although there were no drug-related effects on mortality, both male and female groups were terminated early (i.e., Week 103 and Week 101, respectively) because the number of surviving animals in the respective control groups reached ≤20. At the end of the study period, mean body weights for high dose males and females were 5.9% and 17.7% lower, respectively, compared to control animals. There were no statistically significant drug-related tumor findings in male or female rats. The most notable non-neoplastic histopathology findings were dilated lymphatics in the gut-associated lymphoid tissue (GALT) and small intestine (ileum and jejunum), which were also evident in the general toxicology studies up to 6 months with rats. VX-661 AUC exposure at the high dose (50 mg/kg/day in males and 75 mg/kg/day in females) was 180 and 337 mcg*hr/mL, in males and females, respectively, resulting in exposure margins about 2.4-fold and 4.5-fold above the clinical dose.

Mouse Carcinogenicity Study
In a 26-week oral carcinogenicity study, Tg.rasH2 male and female mice received doses of 0, 30, 100, and 500 mg/kg/day VX-661 (25/sex/group) and 1000 mg/kg/day of the positive control urethane (10/sex/group). There was a statistically significant dose response relationship in mortality for high dose males (76% survival) compared to control males (96% survival). There were no statistically significant drug-related tumor findings in male or female mice. VX-661 AUC exposure at the high dose (500 mg/kg/day) was about 93 and 154 mcg*hr/mL in males and females, respectively.

Executive CAC Recommendations and Conclusions
<u>2-Year Sprague-Dawley Rat</u>

- The Committee concurred that the study was adequate, noting prior Exec CAC approval of the protocol.

- The Committee concurred that there were no drug-related neoplasms in the 2-year rat carcinogenicity study in either males or females.

26-Week Tg.rasH2 Mouse

- The Committee concurred that the study was adequate, noting prior Exec CAC approval of the protocol.

- The Committee concurred that there were no drug-related neoplasms in the 26-week Tg.rasH2 mouse study in either males or females.

Human metabolites >10% of total systemic exposure

- Based upon feasibility and the completed carcinogenicity studies with VX-661 in Sprague-Dawley rats and Tg.rasH2 mice, the Committee concurred that no further studies were required for the safety qualification of the M1, M2, and M5 metabolites with respect to carcinogenicity.

Karen Davis Bruno, PhD
Chair, Executive CAC

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/s/

STEPHANIE J QUINN
11/21/2017

KAREN L DAVIS BRUNO
11/21/2017

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. Please refer to the following for the Mid-Cycle Communication agenda and additional discussion topics:

Mid-Cycle Communication Agenda:

1. Significant Issues: We acknowledge the e-mail request made on October 25, 2017, by Vertex employee Nia Tatsis to allot time for discussion of the results from Study 109 at the mid-cycle teleconference.
2. Information Requests: See "Other Discussion Topics" below.
3. Major Safety Concerns/Risk Management: No major safety concerns have been identified at this time and currently, we see no need for REMs.
4. Advisory Committee Meeting: No Advisory Committee Meeting is scheduled at this time.
5. Late Cycle meeting: Scheduled for December 19, 2017

Other Discussion Topics:

Please refer to the attached slides in which there are questions posed regarding the methodology employed in the in vitro experiments. Your responses to these questions can be discussed at the mid-cycle teleconference or, if you need additional time, at a later date.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 10/27/17

Initialed by: LJafari 10/30/17
ADurmowicz 10/27/17

Finalized by: JLee 10/30/17

Questions regarding the design and data analysis methods of Ussing chamber/FRT experiments in support of NDA 210491

Requested participants: Vertex electrophysiology scientists involved in the design, collection, and analysis of the FRT Ussing chamber experiments that were submitted in response to information request dated 9/1/17

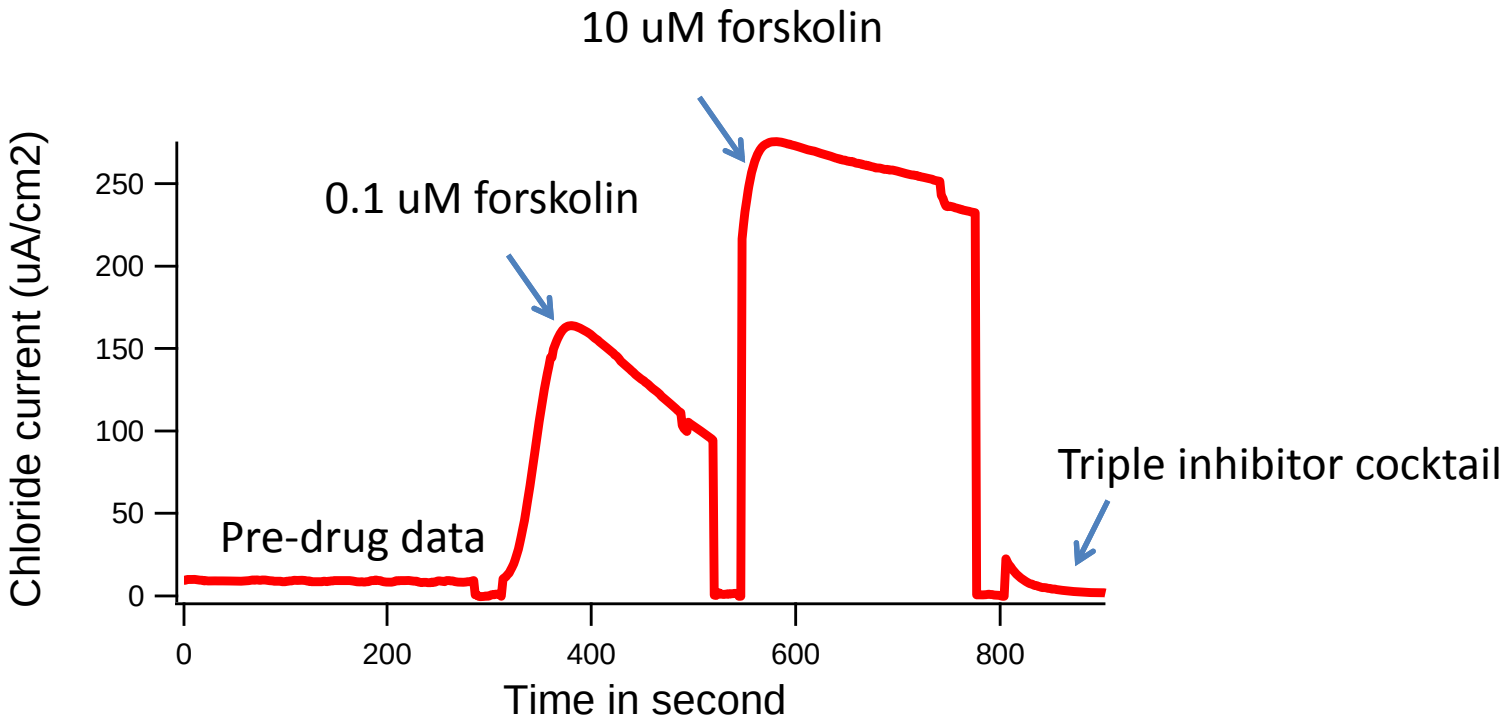
Chloride current data evaluation

- Vertex submitted Ussing chamber/FRT experiments for 6 mutant CFTRs (P67L, A455E, S549R, F1074L, R347H, and D1270N).

- Experiments were run on 96-well Ussing chamber platform. Each well received one treatment condition (chronic application of IVA, TEZ, IVA/TEZ combo for 18-24 hrs prior to recording of forskolin-activated CFTR current). At the end of the experiment a triple inhibitor cocktail was used to suppress the chloride current.

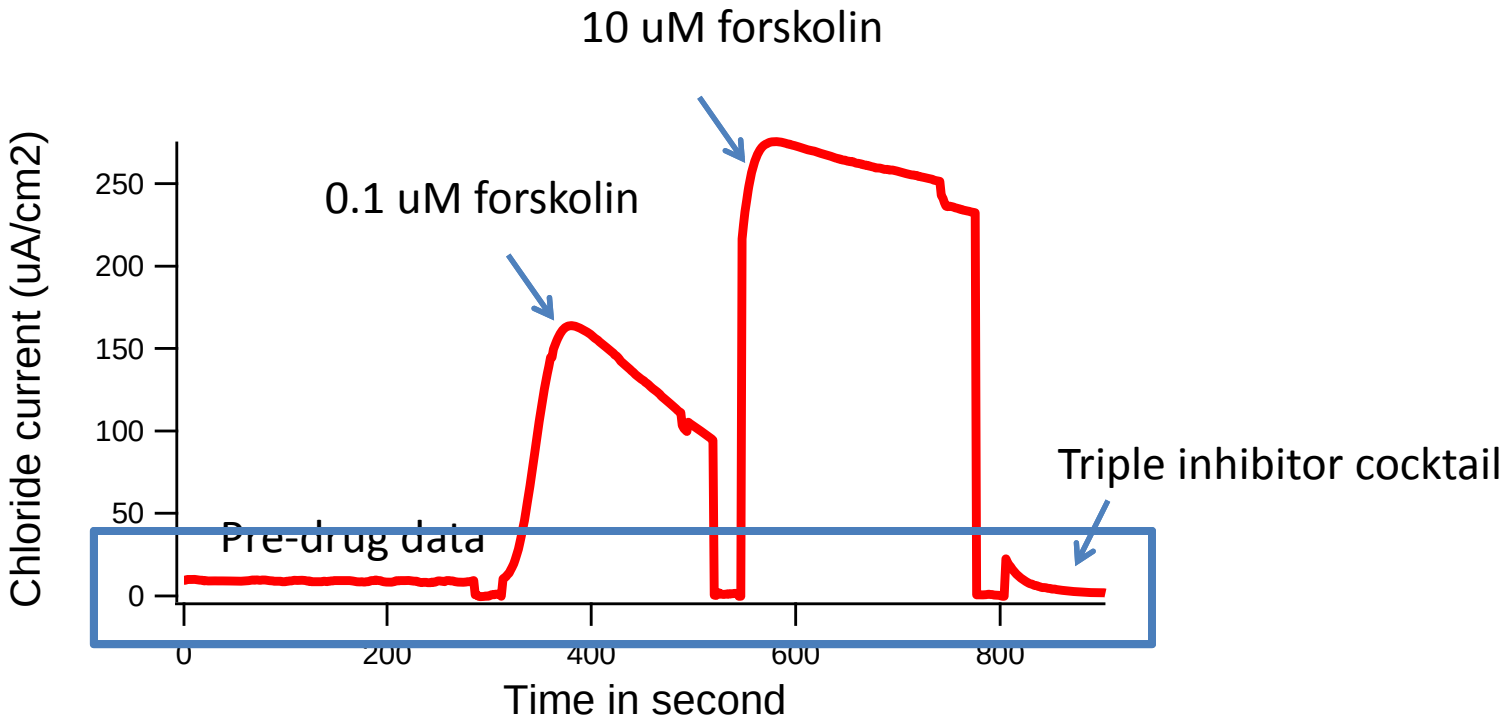
- FDA imported data into Igor Pro analysis software to construct time course plot of each well, visually inspected traces for recording quality/degradation, then performed analysis to extract peak values according to Vertex instruction in Appendix 1.

Example trace from a well in a P67L plate



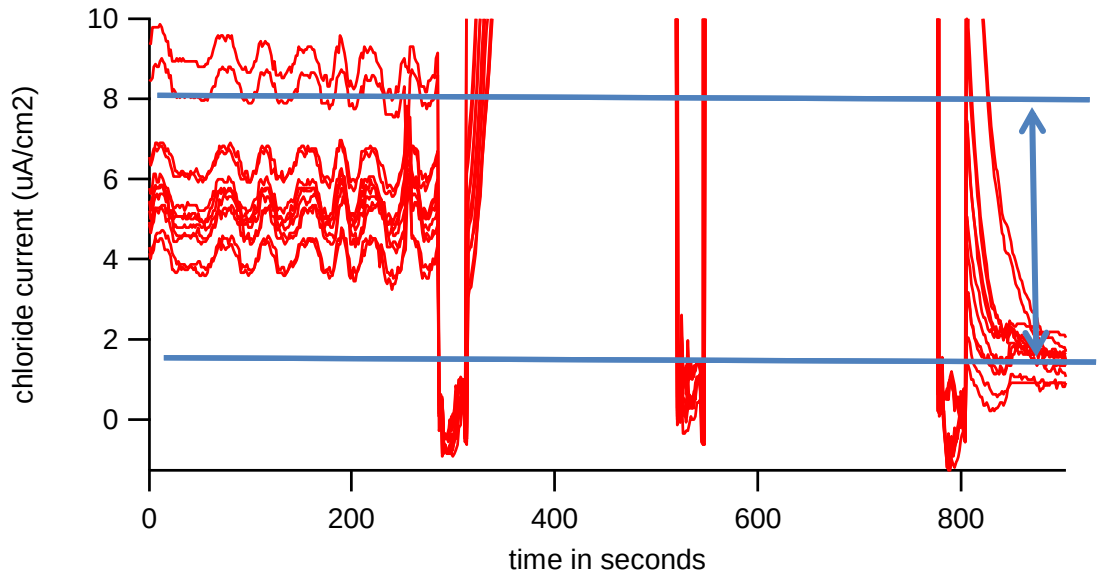
To calculate the peak of drug effect, the sponsor used the triple inhibitor cocktail value as baseline. Previously (study G205), the sponsor used pre-drug data for baseline. In all cases, the triple inhibitor cocktail reduced chloride current to below the pre-drug baseline.

Example trace from a well in a P67L plate



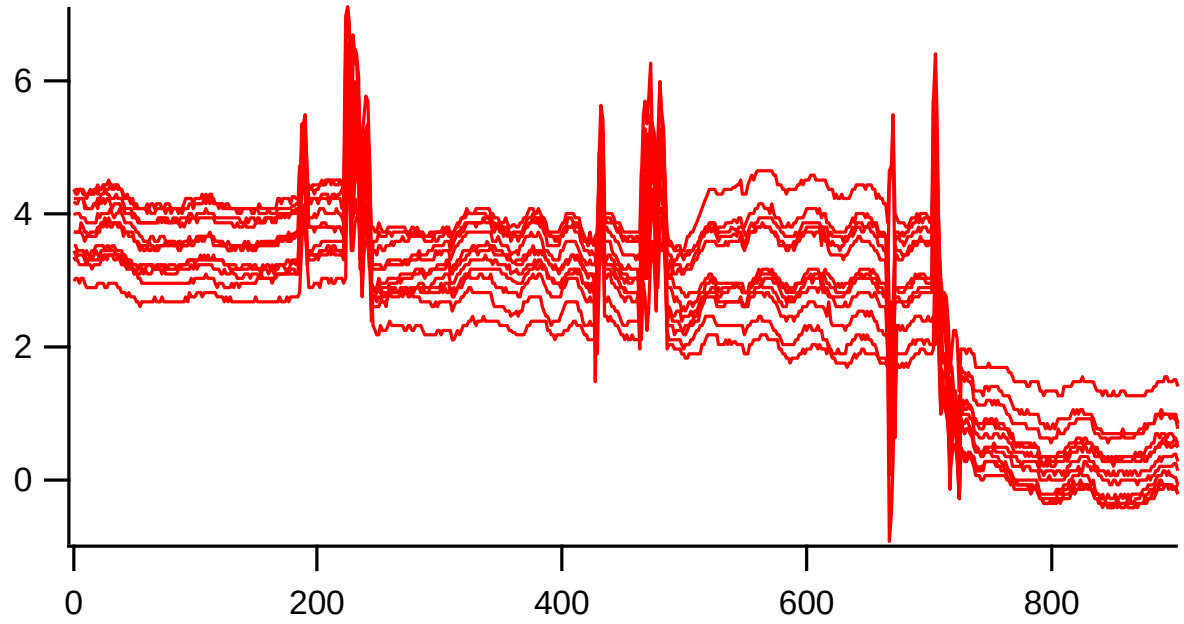
To calculate the peak of drug effect, the sponsor used the triple inhibitor cocktail value as baseline. Previously (study G205), the sponsor used pre-drug data for baseline. In all cases, the triple inhibitor cocktail reduced chloride current to below the pre-drug baseline.

Inhibitors reduced baseline current



Shown are 12 traces of data (one row, including the well used in preceding example) from a P67L plate. Note triple inhibitor cocktail reduced current amplitude to below the pre-drug baseline.

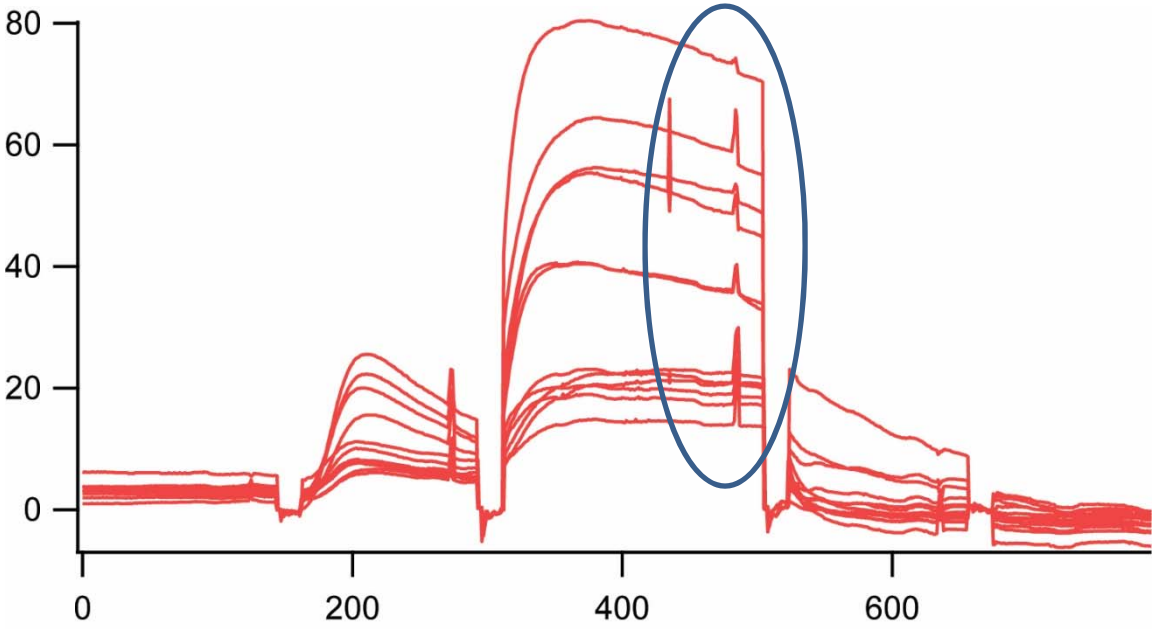
S549R TEZ gradient no IVA



Example from one row of S549R plate. Even when no apparent CFTR current was induced following forskolin application, triple inhibitor cocktail still further reduced background current, suggesting non-CFTR specificity.

According to the data submitted, these recordings (and others of similar quality) were used to calculate values for S549R in Table 3 of study N092. While there is evidence that the sponsor excluded some bad data, others were included in the final report.

Avoid counting aspiration noise CFTR signal



Questions / Discussion

- Please justify the choice of baseline for peak CFTR current calculation and effect of single (G205) vs. triple inhibitors (M078 and N092) on the FRT system. **Is there evidence that CFTR current is present before forskolin application?** *If the inhibitor cocktail has a non-specific effect on endogenous currents in FRT system, then the pre-drug baseline should be used.*

- Regarding WT chloride transport data (used for normalizing mutant CFTR effects), how were these experiments conducted (e.g., were the tissues incubated in DMSO for 18-24 hrs prior to forskolin application to match experimental conditions)?

- When aspiration spikes are large, please make sure they are not counted as CFTR effects.

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/s/

JESSICA K LEE
10/30/2017

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comment and request for information:

> Given the similar pharmacologically activities between TEZ and its active metabolite M1-TEZ (Section 4.3.2 of pharmacol-written-summary.pdf, Submission 0001) and higher plasma M1-TEZ exposure than TEZ exposure (Section 3.3 in summary-clin-pharm.pdf, Submission 0001), provide information as to whether a 3.5-fold dose reduction in TEZ when the drug is co-administrated with a strong CYP3A inhibitor (such as itraconazole) would decrease efficacy if the efficacy of TEZ is driven by both TEZ and M1-TEZ.

Provide your response by November 3, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: NZheng 10/20/17

Initialed by: LJafari 10/20/17

Finalized by: JLee 10/20/17

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/s/

JESSICA K LEE
10/20/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/18/2017 02:52:20 PM
To: meghan_johnston@vrtx.com
CC: jessica.Lee@fda.hhs.gov
BCC: Bamidele.aisida@fda.hhs.gov
Subject: INFORMATION REQUEST NDA 210491

Please see attached and confirm receipt.

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 |Bamidele.aisida@fda.hhs.gov

Please find the attached documents below:

IR midcycle NDA 210491.pdf
http://panorama.fda.gov/document/download?ID=59e7a12700332970550462e8a871d3d3

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

INFORMATION REQUEST

Vertex Pharmaceuticals Incorporated
Attention: Meghan Johnston
50 Northern Avenue
Boston, MA 02210

Dear Ms. Johnston:

Please refer to your New Drug Application (NDA) dated and received June 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tezacaftor/Ivacaftor Tablets.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by November 8, 2017, to continue our evaluation of your NDA.

1. *Provide justification on the selection of 0.2% SLS in 0.1N HCl rather than* (b) (4) *as dissolution medium for Tezacaftor.*

2. *Note that your proposed dissolution acceptance criteria of "NLT* (b) (4) *% (Q) of the labeled amount of Tezacaftor dissolved in 20 minutes and NLT* (b) (4) *% (Q) of the labeled amount of Ivacaftor dissolved in 30 minutes" is permissive and not supported by the dissolution data from the pivotal clinical batches. The dissolution profile data from pivotal clinical batches support the following acceptance criterion, "NLT* (b) (4) *% (Q) of the labeled amount of Tezacaftor dissolved in 15 minutes and NLT* (b) (4) *% (Q) of the labeled amount of Ivacaftor dissolved in 20 minutes". The above acceptance criterion is recommended for batch release and stability testing of your proposed drug product. Justify your proposed acceptance criteria for both APIs, e.g., with respect to clinical relevance of your proposed specification. Alternatively, update the dissolution specification with the Agency's recommended acceptance criteria accordingly.*

3. *Justify the selection of the input variables included in the Tezacaftor and Ivacaftor PLS models, e.g., how relevant are the individual variables for predicting dissolution of each API.*

4. *Provide justification on the threshold set for* [redacted] *of Tezacaftor and Ivacaftor PLS model. Provide plots of the* [redacted] *statistics for detecting samples that are unusual due to "extreme" values in the input data (e.g., hardness,* [redacted] *particle size).*

5. *In your response dated 09/05/2017, your verification of the RTRT dissolution models was based on the dissolution results at 20 minutes for Tezacaftor and at 30 minutes for Ivacaftor. Provide additional verification data at other time points (e.g., Q=* [redacted]*% at 15 minutes for Tezacaftor and Q=* [redacted]*% at 20 minutes for Ivacaftor) for the design space confirmation runs on the* [redacted] *the development batches, the independent test set and/or other relevant batches.*

6. *Provide additional verification data to demonstrate the capability of the model to detect nonconforming batches (e.g., batches with slower dissolution, f2 <50 when compared to the target dissolution profile or batches cannot meet the recommended dissolution acceptance criterion) and what the feedback steps are.*

7. *The commercial manufacturing process description for the tablet in Section 3.2.P.3.3 has insufficient information about the proposed commercial manufacturing process. Update the NDA to include the following:*

    a. *As* [redacted] *is an integral part of the control strategy, in the Process Flow Chart for the tablet in 3.2.P.3.3, include the* [redacted] *as well as the proposed approach for* [redacted].

    b. *Provide the revised/currently proposed master batch record (MBR). Note, this would be a one-time submission of the MBR to the application, and future post – approval changes to the MBR would follow the typical post-approval reporting process for changes to an approved application (e.g., supplements and annual report).*

8. *Currently you have only provided in the NDA a generic description of the* [redacted] *with no details specific to this product. Provide the following information pertinent to this specific product in the Pharmaceutical Development Section to support your* [redacted].

    a. *A summary of design and results of your* [redacted]*;*

b. *Your justification for the proposed* (b) (4)*. Given the observed underweight PKs in your commercial scale batches, justify the adequacy of the* (b) (4) *in case of underweight PKs.*

9. *You have proposed a design space of* (b) (4)*. However, as observed during the Agency's pre-approval inspection, you established* (b) (4) .

10. *Your in-process control (IPC) limits* (b) (4) *in 3.2.P.3.4 are not adequately justified. We acknowledge that you have conducted univariate studies to evaluate the effect of* (b) (4)*. However, you have not provided multivariate experimental data to demonstrate that the* (b) (4) *in the proposed ranges have no impact on product quality (e.g. Dissolution). Therefore, we are concerned about the potentially cumulative effect of off-target* (b) (4) *on tablet CQAs (e.g. Dissolution). We consider it necessary to* (b) (4) *to control the risks. We request that you* (b) (4) *the IPC limits based on your commercial scale experience to date. Examples of suggested ranges are listed below based on our observation of your commercial scale batch data at the pre-approval inspection:*

a. (b) (4)

b.

c.

11. *The tablet in-process controls (IPCs) in 3.2.P.3.4 are not adequate.*

a. *We acknowledge that you included in-process control sampling plan summary in 3.2.P.2.3 Manufacturing Process Development – Introduction to Process Controls and RTRT. Include the IPC sampling plan in P.3.2.3.4 as well.*

b. (b) (4)

12. *Include the amount of* (b) (4) *in the tablet batch formula in 3.2.P.3.2. In addition, any excess amount of materials to be used should be indicated in the batch formula and justified.*

13. *Regarding the* (b) (4) *to manufacture* (b) (4)*, explain why* (b) (4) *was not included in the QbD experiment designs and in 3.2.P.3.3.*

14. *Address the following with regards to your Comparability Protocol:*

(b) (4)

15. *In the event that you revised the dissolution specification as recommended by the Biopharmaceutics team, provided re-assessment on the impact of revised dissolution specification on the criticality and design space of the process parameters and material attributes.*

16. (b) (4) *Specify the equivalent equipment and provide data to demonstrate equivalence or remove the word "equivalent" from the PAT analytical procedure in Module 3.2.P.5.2.*

17. *PLS and PLS-DA chemometric models were developed across the design space. Include summary tables which list DS, excipients and manufacturing process parameters used for the model calibration.*

18. [redacted] (b) (4)

19. *Regarding the PAT method validation, describe how the off-target reference samples were prepared.*

20. *Include the target rate and minimal sampling plan for RTRT in your master batch record and Module 3.2.P.5.*

21. *Regarding the PAT method validation, the acceptance criteria for the accuracy error defined in Module 3.2.P.5.3 are not consistent with those described in SOP-0661. Clarify it to keep consistency.*

22. *The submitted Comparability Protocol* [redacted] (b) (4) *The appropriate category will be determined at the time of filing based on on criteria described in "FDA Guidance for Industry; Changes to an Approved NDA or ANDA (April 2004).*

If you have any questions, call me at (240) 402-2691.

Sincerely,

{See appended electronic signature page}

Florence Aisida, Pharm. D, BCPS
Regulatory Business Process Manager,
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Florence Aisida

Digitally signed by Florence Aisida
Date: 10/18/2017 02:47:14PM
GUID: 555a34d1000660027d762f4430d19ca0

Dear Ms. Heyman,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following comments:

> "Submit a revised ADSL dataset that includes a variable for CF genotyping for each subject and the statistical program for Study VX14-661-107."

Provide your response by October 11, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: SChin 10/3/17
JLee 10/4/17

Initialed by: Ljafari 10/4/17
Adurmowicz 10/4/17

Finalized by: JLee 10/4/17

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/s/

JESSICA K LEE
10/04/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/02/2017 10:49:07 AM
To: Alissa_Minkoff@vrtx.com
CC: Jessica.Lee@fda.hhs.gov
BCC: Bamidele.aisida@fda.hhs.gov
Subject: INFORMATION REQUEST NDA 210491

Hello Alissa,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by November 2 ,2017

1.Provide test procedures for the specifications of the (b) (4) starting materials, (b) (4) for Tezacaftor.

2.Provide the test procedures for the isolated intermediate (b) (4), and clarify how they were validated.

3.You have not submitted any characterization data on the potential and actual impurities in Tezacaftor. Submit at least one reliable structure elucidation data on each of the impurities.

4.You have not demonstrated that your Assay and Degradation Products method for Tezacaftor can resolve the impurity (b) (4) from other impurities or can quantify this impurity. We also note that the Assay and Degradation Products method shows the peaks due to the following impurities unresolved: (b) (4), and that for only (b) (4) there is a separate method. Thus, your total validation package for the methods for organic impurities in the drug substance is inadequate. The total validation package should include all specified impurities and the impurities that are monitored as unspecified impurities, including (b) (4) which are due to the starting material (b) (4).

5.Submit your qualification information on the impurity reference standards that were needed for the validation of the test methods for the impurities in Tezacaftor.

6.Your submitted (b) (4) stability data on the drug substance do not support the proposed retest period ((b) (4) months) for the “NMT (b) (4) °C” shelf-life storage condition. Submit (b) (4) data or revise the shelf-life storage condition to “Store at (b) (4); excursions permitted between (b) (4)”.

Please confirm receipt of this email.

Thanks,

Florence Aisida, Pharm.D,BCPS
RBPM, Office of Program and Regulatory Operations
Office of Pharmaceutical Quality/CDER/FDA.
(240) 402-2691 |Bamidele.aisida@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

ATTENTION: Charlotte Heyman
Senior Manager, Regulatory Affairs

Dear Ms. Heyman:

Please refer to your New Drug Application (NDA) dated and received June 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tezacaftor/Ivacaftor; Ivacaftor Tablets, 100 mg/150 mg; 150 mg.

We also refer to your correspondence, dated and received June 28, 2017, requesting review of your proposed proprietary name, Symdeko.

We have completed our review of the proposed proprietary name, Symdeko, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 28, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Jessica K. Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
09/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Vertex Pharmaceuticals Inc.
50 Northern Ave.
Boston, MA 02210

Attention: Alissa Minkoff, MS
Manager, Regulatory Affairs

Dear Ms. Minkoff:

Please refer to your New Drug Application (NDA) dated June 28, 2017, received June 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Tezacaftor/Ivacaftor Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 28, 2018. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

During our filing review of your application, we identified the following potential review issues:

Clinical/Clinical Pharmacology:

1. Whether or not *in vitro* data alone provides sufficient evidence for the efficacy of the tezacaftor/ivacaftor combination in patients with gating mutations known to be responsive to ivacaftor will be a review issue. In that light, we recommend that you submit clinical data from Study VX14-661-109 when it becomes available to support the added benefit of tezacaftor in this population.

Nonclinical:

2. (b) (4) Submit any new data or other justification that address our concerns with the proposed established pharmacologic class for tezacaftor. In addition, summarize available data or other justification to support describing the pharmacological activity of tezacaftor as (b) (4)

(b) (4) as stated in Section 12.1 of your draft labeling. The final pharmacologic class will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide any available stability data for tezacaftor drug substance manufactured at the (b) (4) commercial site.

2. Provide the quantitative composition of the (b) (4) film coat, or provide a Letter of Authorization allowing our review of a drug master file from (b) (4) that contains this formation.

3. Three mutations (R347H, G1069R, R1070Q) listed in section 12.1 of the Kalydeco labeling are not included in the Tezacaftor/Ivacaftor labeling. You have provided the rationale for not including R347H in study report M078. Provide a rationale as to why the G1069R and R1070Q mutations should not be included in Table 4. of the proposed product labeling.

4. For the six CF-causing mutations listed below, provide complete data for all in vitro experiments conducted in Ussing chambers with FRT cells. In addition provide the matching Western Blot data. Only the data reported in study M078 or study N092 should be supplied. Data should be supplied from individual experiments/chambers and not averaged. The data should be supplied in an electronic file format that allows FDA to recapitulate the entire experiment: data should be supplied arranged in 3 columns at a minimum: column 1 – time; column 2 – current; column 3 – entry at the time each solution was applied. Please note specific units for the time and current parameters. Datasets for FRT in vitro studies should allow for reconstruction of time course plot (control, CFTR agonist, potentiator and inhibitor applications). These data will allow FDA to evaluate inter-experiment baseline and the % potentiation variability. We request the FRT data for the following mutants: P67L, R347H, A455E, S549R, D1270N and F1074L.

5. WB data were not located for three mutations: G551S, S1255P, G1349D. Submit or provide an explanation of why the WB data are not available.

6. Submit summary chloride channel and/or WB data you may have on any nonresponsive mutations (i.e. those enrolled in study 107) using the combination of TEZ/IVA.

7. Explain why the A1067T mutation was not considered an eligible mutation for study 108 enrollment.

8. Provide primary endpoint results by mutation for study 108.

9. In the Ussing chamber experiments, a mixture of three inhibitors (PPQ-102, GlyH-101 and CFTR inhibitor 172) was used to block the chloride current. In the in vitro experiments for ivacaftor only (G205) only a single inhibitor was used. Provide your technical rationale for this change in experimental design.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line.

2. White space should be present before each major heading in HL.

3. If no Contraindications are known, this section must state "None."

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 15, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
09/01/2017

Dear Ms. Minkoff,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following request:

> For Study VX14-661-106, provide patient data listing information as mentioned in our information request dated August 18, 2017, for these additional clinical sites: James Wallace, M.D. (Site #117, South Dakota) and Amparo Sole Jover, M.D. (Spain Site #533, Valencia, Spain).

Provide the requested information by August 28, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: AOrencia 8/23/17
JLee 8/23/17

Initialed by: LJafari 8/23/17

Finalized by: JLee 8/23/17

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/s/

JESSICA K LEE
08/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

PRIORITY REVIEW DESIGNATION

Vertex Pharmaceuticals Inc.
50 Northern Ave.
Boston, MA 02210

Attention: Alissa Minkoff, MS
Manager, Regulatory Affairs

Dear Ms. Minkoff:

Please refer to your New Drug Application (NDA) dated June 28, 2017, received June 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Tezacaftor/Ivacaftor Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is February 28, 2018.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 9, 2018.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 10, 2017.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
08/23/2017

From:	Aisida, Bamidele (Florence)
To:	"Alissa_Minkoff@vrtx.com"
Cc:	Lee, Jessica K (ODEII/DPARP)
Subject:	NDA 210491 IR 8-21-17
Date:	Monday, August 21, 2017 9:44:24 AM

Hello Alissa,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by September 5 ,2017

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

Please confirm receipt of this email.

Thanks,

Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following requests for information:

1. Submit the study subject data listing grouped as pdf files, stratified (organized) by clinical study investigator site separately (i.e., all requested information for *a* through *f* below, in one pdf file, for each principal investigator site). Also, provide the principal investigator's most recent contact information.

2. Provide the following study subject data listings (*a* through *f* below) for, grouped by Principal Investigator/study site: VX14-661-108 Site 020 (T. G. Liou, M.D.), VX14-661-107 Site 51 (C. Keating, M.D.), VX14-661-108 Site 51 (E. DiMango, M.D.), and VX14-661-106 Site 39 (D. Quintero, M.D.).

    a. Subject discontinuations (If applicable, per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).

    b. Subject assignment per treatment arm (randomization group, if applicable).

    c. Concomitant medication list (non-study medications).

    d. All adverse events (If applicable pretreatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no])).

    e. Protocol deviations or violations.

    f. Primary study efficacy endpoint/s. [Note: Submit per patient per study visit: FEV1, CFQ-R, pulmonary exacerbations, and sweat chloride. For BMI, provide baseline & end of study treatment visit/last recorded BMI].

Otherwise, submit any relevant documents, as deemed necessary (e.g., provide full explanation, if final applicant-CRO primary efficacy raw data point(s) was/were different from the study site. Also, provide adequate documentation on the edits that were made before the data lock).

Your response will need to be submitted officially to the NDA by August 28, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: A Orencia 8/18/2017
S Chin 8/18/2017

Cleared by: L Jafari 8/18/2017

Finalized by: E Sit 8/18/2017

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/s/

ELAINE SIT
08/18/2017
Signed on behalf of Jessica Lee

Dear Ms. Minkoff,

Your submission dated June 28, 2017, to NDA 210491, is currently under review. We have the following request:

> With regard to Study Report VX15-661-010, please upload all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com

Provide the requested information by August 7, 2017. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: QT/IRT 8/1/17
JLee 8/1/17

Initialed by: NTon for LJafari 8/1/17

Finalized by: JLee 8/1/17

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/s/

JESSICA K LEE
08/01/2017

From:	Aisida, Bamidele (Florence)
To:	"Alissa Minkoff"
Cc:	Lee, Jessica K (ODEII/DPARP)
Subject:	NDA 210491 IR 7-28-17
Date:	Friday, July 28, 2017 7:57:42 AM

Hello Alissa,

Please provide an English translation to the executed batch record for tezacaftor (b) (4).

Please confirm receipt of this email and respond to the question by August 1,2017.

Thanks,
Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

From:	Aisida, Bamidele (Florence)
To:	"Alissa Minkoff"
Cc:	Lee, Jessica K (ODEII/DPARP)
Subject:	RE: NDA 210491 IR 7-20-17
Date:	Thursday, July 20, 2017 1:59:15 PM

Hello Alissa,

Please submit a representative executed batch record for the manufacture of the (b) (4) for their N210491?

Please confirm receipt of this email and respond to the question by July 27,2017.

Thanks,
Florence

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

NDA ACKNOWLEDGMENT

Vertex Pharmaceuticals Inc.
50 Northern Ave.
Boston, MA 02210

Attention: Alissa Minkoff, MS
Manager, Regulatory Affairs

Dear Ms. Minkoff:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Tezacaftor/Ivacaftor Tablets

Date of Application: June 28, 2017

Date of Receipt: June 28, 2017

Our Reference Number: NDA 210491

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 27, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JESSICA K LEE
07/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

PROPRIETARY NAME ACKNOWLEDGEMENT

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

ATTENTION: Alissa Minkoff, MS
Manager, Regulatory Affairs

Dear Ms. Minkoff:

Please refer to your New Drug Application (NDA) dated and received June 28, 2017 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tezacaftor/Ivacaftor Tablet, 100 mg/150 mg and Ivacaftor Tablet, 150 mg.

We acknowledge receipt of your correspondence, dated and received June 28, 2017, requesting a review of your proposed proprietary name, Symdeko.

If the application is filed, the user fee goal date will be September 26, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Jessica Lee, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Michael Sinks, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MICHAEL A SINKS
07/10/2017

From:	Aisida, Bamidele (Florence)
To:	"Alissa Minkoff"
Cc:	Lee, Jessica K (ODEII/DPARP)
Subject:	RE: NDA 210491 IR 7-6-17
Date:	Friday, July 07, 2017 10:16:28 AM

Hello Alissa,

I have another question from the CMC team.

Please explain why you haven't submitted executed batch records as required per the regulation 21 CFR 314.50(d)(1)(i)(*b*).

Please confirm receipt of this email and respond to the question by July 10,2017.

Thanks,
Florence

From: Alissa Minkoff [mailto:alissa_minkoff@vrtx.com]
Sent: Thursday, July 06, 2017 12:37 PM
To: Aisida, Bamidele (Florence)
Cc: Lee, Jessica K (ODEII/DPARP)
Subject: RE: NDA 210491 IR 7-6-17

Hello Ms. Aisida,

I confirm receipt of your email.

Many thanks,
Alissa

Alissa Minkoff, MS
Manager, Regulatory Affairs
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210
tel: 617.961.0003
alissa_minkoff@vrtx.com
www.vrtx.com

From: Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]
Sent: Thursday, July 06, 2017 10:52 AM
To: Alissa Minkoff
Cc: Lee, Jessica K (ODEII/DPARP)
Subject: NDA 210491 IR 7-6-17

Hello Ms. Minkoff,

Please confirm that Vertex is cross-referencing NDA 203188 for all ivacaftor (b) (4)

information? A confirmation in the cover letter is fine.

Please confirm receipt of this email and respond to the question by July 10,2017.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

From:	Aisida, Bamidele (Florence)
To:	"Alissa_Minkoff@vrtx.com"
Cc:	Lee, Jessica K (ODEII/DPARP)
Subject:	NDA 210491 IR 7-6-17
Date:	Thursday, July 06, 2017 10:51:41 AM

Hello Ms. Minkoff,

Please confirm that Vertex is cross-referencing NDA 203188 for all ivacaftor (b) (4) information? A confirmation in the cover letter is fine.

Please confirm receipt of this email and respond to the question by July 10,2017.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108105

MEETING MINUTES

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA, 02210

Attention: Alissa Minkoff, MS
Manager, Regulatory Affairs

Dear Ms. Minkoff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tezacaftor (VX-661) & ivacaftor (VX-770).

We also refer to the meeting between representatives of your firm and the FDA on May 30, 2017. The purpose of the meeting was to discuss clinical data to support a NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Angela Ramsey M.P.H., M.S.N., R.N.
Senior Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: PreNDA

Meeting Date and Time: May 30, 2017
Meeting Location: FDA White Oak, Building 22, Conference Room 1309

Application Number: 108105
Product Name: tezacaftor (VX-661) & ivacaftor (VX-770)
Indication: Treatment of CF patients 2 and older with mutations in CFTR gene
Sponsor/Applicant Name: Vertex Pharmaceuticals

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.,
Meeting Recorder: Angela Ramsey

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lim, Robert, M.D., Clinical Reviewer
Anthony Durmowicz, M.D., Clinical Team Leader
Lawrence Leshin, Ph.D., Nonclinical Reviewer
Marcie Wood, Ph.D., Non-Clinical Team Leader
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer
Anshu Marathe, Ph.D., Clinical Pharmacology Team Leader
Craig Bertha, Ph.D., CMC Lead
Angela Ramsey, Project Manager

SPONSOR ATTENDEES

Antoinette Paone, MS, MBA Vice President, Global Regulatory Affairs
Gemma Pilkington Director, Global Regulatory Affairs
Alissa Minkoff, MS Manager, Global Regulatory Affairs
Charlotte McKee, MD Vice President, Clinical Development
Edward Ingenito, MD Sr. Medical Director, Clinical Development
Julie Lekstrom Himes, MD Sr. Medical Director, Clinical Development
Christopher Simard, MD Sr. Director, Global Patient Safety
Varun Garg, PhD Sr. Director, Clinical Pharmacology
Fred Van Goor, PhD Sr. Research Fellow, Biology
Bo Yang, PhD Vice President, Biometrics
Yimeng Lu, PhD Director, Biometrics
Graeme Smith, PhD Vice President, Pharmaceutical & Preclinical Sciences

Joseph Prezioso, PhD Nonclinical Development Fellow II, Preclinical Safety Assessment

BACKGROUND

Vertex submitted a Type B meeting request dated, March 16, 2017 to discuss their clinical data to support a NDA submission for tezacaftor (VX-661)/ivacaftor (VX-770) in the treatment of cystic fibrosis patients 2 years and older with mutations in the CFRT gene. Vertex submitted background material dated, April 26, 2017. Upon review of the material, the Division responded via secure email on May 26, 2017. Vertex requested to continue with the face-to-face meeting to discuss responses to questions 1, 2, 3 & 7. Vertex provided handouts to assist with the meeting (see attachment).

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant responses. The sponsor's questions are in bold italics; the Division responses are in italics; and discussion is in normal font.

DISCUSSION

Question 1:
Does the Division agree that the proposed clinical data package is sufficient to support the NDA submission for TEZ/IVA combination therapy?

FDA Response:
Yes, we agree that the proposed clinical package is sufficient to support the filing and review of the TEZ/IVA combination

Whether further information is to support approval will be a review issue. In addition, we have the following comments regarding the clinical pharmacology program:

1. *The population PK analysis should assess the impact of the presence of tezacaftor on ivacaftor PK.*

2. *As discussed during the End-of-Phase 2 (EOP2) meeting, the bridge of the 100/150 mg fixed dose combination formulation to earlier separate tablets formulation would be a review issue, pending the result of Study 004 and dissolution data. Thus, the actual clinical pharmacology information that could be included in the label from earlier formulations will be a review issue.*

Discussion:
Vertex referenced slides 4-6, stating that the ivacaftor exposure increased slightly when coadministered with TEZ, but it has no significant impact on clinical outcomes.

The Division acknowledged sponsor's PK findings in study 770-017 and 661-108, and clarified that the population PK analysis regarding the impact of tezacaftor on ivacaftor PK would assist in labeling for TEZ/IVA. The Division recommended that the population PK analysis should include all available information from different studies, including study 017 and 108.

The sponsor confirmed that the pop PK analysis will be in the filing submission.

Question 2:
Does the Division agree that TEZ contributes to the overall effect of TEZ/IVA combination therapy?

FDA Response:
This is a review issue; however, based on the limited clinical information included in the meeting package, TEZ appears to contribute to the overall effect of the TEZ/IVA combination. Include in your NDA submission rationale/justification, as well data to support how the TEZ/IVA development program addressed the contribution of each component to the TEZ/IVA combination.
Also, as discussed during EOP2 meeting, the submission should clarify that efficacy observed from the TEZ/IVA combination product is not due to increased systemic exposure of either of the two drugs.

Discussion:
Vertex referenced slide 6, and suggested that the current ivacaftor dose/exposure has reached the plateau in the PK/PD analysis for G551D mutation, and that the slight increase (~17%) of ivacaftor exposure in presence of TEZ was not expected to achieve additional efficacy.

The Division acknowledged sponsor's PK/PD analysis for the G551D mutation, and stated that similar analysis for ΔF508/Residual Function (RF) mutations would be helpful to assist the review.

The sponsor confirmed that the PK/PD analysis for RF mutations will be in the filing submission.

Question 3:
Does the Division agree with the proposed indication statement?

FDA Response:
The wording of the indication statement is a review issue. However, the approach taken would likely be similar to that taken in the ivacaftor sNDA 203188 S019, provided similarly convincing supportive in vitro data for the TEZ/IVA combination are submitted. If you plan on relying on in vitro assays/data to support this application, for the in vitro assays used, the data submitted should to be of the same quality and extent as that submitted for the in vitro assays used support ivacaftor sNDA 203188 S019.

Your NDA submission should also include rationale and data to support how responsiveness to TEZ/IVA was determined and how in vitro responsiveness to TEZ/IVA was differentiated from in vitro responsiveness to IVA alone.

(b) (4)

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Discussion
Vertex referenced slides 8-10 and stated that they planned on relying on both in vitro and clinical data to support responsiveness. For mutations not clinically studied, in vitro data would be used and the assay methods and data quality would be similar to that submitted with ivacaftor sNDA 203188 S019. Clinical support would consist of results from studies 106, 107, and 108 as well as phase 2 results from *G551D* patients receiving TEZ/IVA. The Division stated that the submitted data would have to demonstrate that TEZ/IVA offered an additional benefit above IVA alone, whether it be based on in vitro data, clinical data, or both. The Division further stated that not all mutations approved for IVA alone would necessarily be approved for TEZ/IVA, unless TEZ/IVA demonstrated added benefit above IVA. Vertex understood and stated that, for the proposed 'responsive' mutations, either clinical data would demonstrate an incremental clinical benefit of TEZ/IVA above IVA and/or in vitro data would demonstrate an incremental benefit in terms of in vitro responsiveness. The Division noted that Vertex should carefully consider and justify what increase in in vitro responsiveness (i.e., increase chloride transport) would be considered sufficient to conclude that TEZ/IVA provided an added benefit above IVA alone. Vertex stated that they intend on submitting in vitro assay data late June/early July. The FRT model will be included in the submission as well as clinical data studies 106, 107, and 108). The Division asked when results from study 109 (*F508del*/ "gating") would be available to which Vertex stated October/November.

Question 4:
Does the Division agree that the proposal described is sufficient for meeting the requirements for an ISE and ISS?

FDA Response:
Yes, we agree.

Discussion:
No discussion occurred.

Question 5:
Does the Division agree that Studies 106, 108, and 101 to support the demonstration of efficacy, and Studies 101, 103, 106, 107, 108, and 110 to support safety in the target populations, are considered the covered studies for this NDA under 21 CFR 54 for purposes of Financial Disclosure?

FDA Response:
Yes, we agree.

Discussion:
No discussion occurred.

Question 6:
Does the Division agree that TEZ/IVA meets the requirements for a Priority Review?

FDA Response:
This determination will be made at the time of NDA submission. However, we anticipate that this will be a Priority Review.

Discussion:
No discussion occurred.

Question 7:
If the NDA filing for TEZ/IVA combination therapy is granted Priority Review, Vertex is anticipating providing the safety update per 21 CFR 314.50(d)(5) to the Division no later than 90 days after the initial NDA submission. Does the Division agree with this timing for the safety update? Does the Division agree with the proposed content of the safety update?

FDA Response:
If Priority Review is granted, the proposed timeline for the submission of the safety update is reasonable. In the safety update and the NDA submission, include narratives and CRFs for all SAEs. Otherwise, pending review, the proposed content of safety update appears acceptable.

Discussion: (see slide 7):
Vertex proposed not to provide narratives for all exacerbation SAEs that were deemed not related to study drug, but rather just line listings. The Division stated narratives for all SAEs should be provided with the submission, as in the review of safety, especially for a new molecular entity, the Division considers all events regardless of attribution.

Question 8:
Clinical study data will be placed in the SDTM and ADaM folders according to the eCTD file directory structure for study datasets in accordance with FDA Study Data Technical Conformance Guide dated March 2017.To facilitate the review, Vertex plans to submit executable SAS programs in SAS version 9.2 for tables included in the submission for the Phase 3 pivotal studies (106 and 108), the Phase 3 long-term, open-label study (110 interim analysis), the ISE, and the Phase 3 ISS. Is this plan acceptable to the Division?

FDA Response:
The proposal for study data submission is acceptable in general. Provide a define.pdf and well-documented Data Reviewer's Guide with the data submission. Further requests for information will be forwarded if necessary on review of the NDA submission.

Include the code for any macros and any necessary formats that are called or used within these programs.

Discussion:
No discussion occurred.

Question 9:
Would the Division be amenable to hold an Application Orientation Presentation Meeting with Vertex within 30 days after NDA submission?

FDA Response:
We do not anticipate the need for such a meeting provided that the NDA submission is written and structured appropriately.

Discussion:
No discussion occurred.

Question 10:
Does the Division agree that there are no controversial issues with the proposed TEZ/IVA NDA filing that would require a Pulmonary and Allergy Advisory Committee to be convened as part of the NDA review process?

FDA Response:
The need for an Advisory Committee meeting will be determined at the time of NDA submission. However, based on the information provided and pending review of the submission, the Division does not anticipate the need for an Advisory Committee meeting.

Discussion:
No discussion occurred.

Question 11:
Given the high degree of linkage demonstrated between improved in-vitro chloride transport and clinical response with IVA in eight residual function mutations, and with TEZ/IVA in seventeen residual function mutations included in Study 661-108, does the Division agree that the totality of data generated with TEZ/IVA (including in-vitro data in 25 residual function mutations and the clinical data from Study 661-108) and with IVA alone (as described in the Kalydeco sNDA, 203188 S019) support the extrapolation of clinical safety and efficacy from in-vitro data, to the extent necessary, for the eight residual function mutations that were not represented in Study 661-108?

FDA Response:
This will be a review issue. Your NDA submission should include rationale for your proposed approach to extrapolation.

Discussion:
No discussion occurred.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

ATTACHMENTS AND HANDOUTS

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

/s/

ANGELA H RAMSEY
06/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108105

MEETING MINUTES

Vertex Pharmaceuticals Inc.
Attention: Meghan Johnston
Director, Regulatory Affairs CMC
50 Northern Avenue
Boston, MA 02210

Dear Ms. Johnson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-661.

We also refer to the meeting between representatives of your firm and the FDA on May 16, 2017. The purpose of the meeting was to discuss refinements to Vertex's approach to QbD during the development of tezacaftor/ivacaftor drug product, the resulting control strategies, and implementation of process control and real-time release testing (RTRT).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Florence Aisida, Regulatory Project Manager, at (240) 402-2691.

Sincerely,

{See appended electronic signature page}

Florence Aisida, Pharm. D, BCPS
Regulatory Business Process Manager,
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	CMC
Meeting Date and Time:	May 16, 2017, 12:30 PM – 1:30 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 21, Conference Room: 1539 Silver Spring, Maryland 20903
Application Number:	IND 108105
Product Name:	VX-661
Indication:	Treatment of Cystic Fibrosis
Sponsor/Applicant Name:	Vertex Pharmaceuticals Inc.
Meeting Chair:	Julia Pinto
Meeting Recorder:	Florence Aisida

FDA ATTENDEES

Sharmista Chatterjee, PhD., Division Director, Office of Process and Facilities
Sau (Larry) Lee, Ph.D., Deputy Director, ETT Chair, Office of Testing and Research
Anthony Durmowicz MD, Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products
Craig Bertha, Ph.D., Acting Quality Assessment Lead, New Drug Products
Zhigang Sun, Ph.D., Acting Branch Chief, Office of Process and Facilities
Yong Hu, Ph.D., Acting Quality Assessment Lead, Office of Process and Facilities
Hong Yang, Ph.D., Reviewer, Office of Process and Facilities
Debasis Ghosh, Ph.D., QAL, Division of New Drug API, Office of New Drug Products
Christina Capacci-Daniel, Ph.D., Acting Quality Assessment Lead, Division of Inspectional Assessment, Office of Process and Facilities
Florence Aisida, Pharm D., BCPS, Regulatory Business Project Manager
Steven Kinsley, Ph.D., Regulatory Business Project Manager

SPONSOR ATTENDEES

Meghan Johnston, Associate Director, Regulatory Affairs CMC
Carly Evans, Director, Regulatory Affairs CMC
Andrew Kuzmission, Ph.D., Senior Director, Regulatory Affairs CMC
Stephanie Krogmeier, Ph.D., Senior Director, Regulatory Affairs CMC
Eleni Dokou, Ph.D., Senior Director, Formulation Development
Hayden Thomas, Ph.D., Vice President, Pharmaceutical and Pre-Clinical Sciences

Kelly Swinney, Ph.D., Senior Director, Analytical Development
Adam Looker, Ph.D., Director, Process Chemistry
Thomas Gandek, Ph.D., Vice President, Technical Operations
Geny Doss, Vice President, Quality Assurance
Katie McCarty, Scientist, Formulation Development

1.0 BACKGROUND

Vertex Pharmaceuticals, Inc. is planning to file an NDA for tezacaftor/ivacaftor fixed dose combination (FDC) tablets and is developing the FDC as a continuous manufacturing process under a Quality by Design (QbD) paradigm.

FDA sent Preliminary Comments to Vertex on May 11, 2017.

2. DISCUSSION

Question 1: **Is the Agency aligned with our QbD approach and implementation of the proposed control strategy for DS, (b) (4), and drug product including how it is outlined in the submission to facilitate review of the tezacaftor/ivacaftor NDA?**

a) Refinements to Vertex's Approach to Quality by Design (QbD)
b) Control Strategies
c) Continuous Manufacturing and the Implementation of Process Controls and RTRT
d) Roadmap" of Module 3

FDA Response:
In general your QbD approach and the planned presentation, as outlined, appear reasonable. Acceptability of this approach will be determined at the time of NDA review. However, based on the summary information provided, we have the following comments that we would like to discuss at the meeting for additional clarification:

1. *According to Figure 2, your criticality assessment starts with selecting desired manufacturing ranges and thresholds for determining criticality. For the process parameters that are determined to be non-critical, the designation may only apply when the parameters are operated within the "desired manufacturing ranges." Address the following regarding criticality assessment:*

    a. *Indicate if the ranges on which the criticality assessment is based would be documented in the NDA in P.2 section. We note that post-approval changes may require reassessment of criticality for the non-critical process parameters (NCPPs).*

Meeting Discussion:
Vertex clarified the definitions of critical, non-critical statistically significant and non-statistically significant parameters, and described where the NCPP's would be documented in Module 3 and batch records. FDA acknowledges Vertex's reporting plan.

b. *You have indicated that NCPPs would not be included in the process description section. However, omission of information about NCPP's would preclude giving a detailed description of the proposed commercial scale manufacturing process. Please note a complete description of the manufacturing process is needed to evaluate the proposed control strategy.*

Meeting Discussion:
Vertex clarified that NCPPs would be included in sections S.2.6, P.2.3 and the batch record.

c. *Regarding managing excursions of NCPP beyond the previously studied ranges, clarify how the NCPPs will be controlled in your master batch record. Will there be any action limits either manual or automated, when the NCPP are outside the design space limits? It is understood that changes to NCPP would be managed solely under your pharmaceutical quality system as part of the overall control strategy.*

Meeting Discussion:
Vertex stated that they have studied the effects of parameters within the Desired Manufacturing Range (DMR) and plan to run the process within the Design Space Limit (DSL), (b) (4)
Vertex stated that they would study any excursions outside of the DMR and re-evaluate the impact of these parameters. Vertex clarified that for the (b) (4)
.

2. *In referring to Section 7.1.4, please clarify the difference between statistically significant and statistically insignificant non-critical process parameters.*

Meeting Discussion:

Vertex clarified the difference between statistically significant and statistically insignificant non-critical process parameters.

3. *We acknowledge that* (b) (4) .

Meeeting Discussion:
Vertex clarified that (b) (4) **FDA suggests that Vertex include in the submission their rationale for not including specification for particle size.**

4. *Your continuous drug product manufacturing process for Orkambi defined a Product Key (PK) based on* (b) (4) *Clarify how a PK unit is defined* (b) (4) *and provide the rationale for this definition of a PK. Additionally, describe how this is incorporated into the diversion strategy for the isolation of non-conforming material.*

Meeting Discussion:
Vertex clarified that the PK size corresponds to (b) (4)

5. *You state that you plan to submit a comparability protocol with the initial NDA outlining the plans to* (b) (4) *Clarify whether the protocol is for specific changes or is broad in scope.*

Meeting Discussion:
Vertex clarified the comparability protocol (b) (4)

Additional considerations for information to be included in the NDA:

1. *Your QbD approach and implementation of the proposed control strategy for drug substance synthesis appear reasonable. To facilitate review of the NDA, provide summaries of the design of experiments studies conducted. Please note that proposed specification of any individual impurity in drug substance above ICHQ3A qualification threshold level must be qualified to ensure safety. The adequacy of the information will be determined at the time of NDA review.*

2. *Explain how you characterize* (b) (4)

   Meeting Discussion:
   Vertex clarified the characterization of (b) (4) **and acknowledges that** (b) (4) **Vertex will study any excursions outside of the target for these parameters (e.g.** (b) (4)**) to determine the impact on** (b) (4)**.**

3. *Provide information on how the commercial batch size will be defined, including information about line rates and proposed run time.*

   Meeting Discussion:
   Vertex clarified that the commercial batch size is defined by mass, not line-rate or proposed run time.

4. *We recommend that you set a metric for assessing process robustness (e.g., batch yield) in advance.* (b) (4)

   Meeting Discussion:
   Vertex clarified that percent yield acceptance criteria will be established.

5. *It is noted that degradation products are only tested for stability, but not for batch release. Provide justification in the NDA.*

6. *The IPC ranges for the* (b) (4) *should be justified in the NDA.*

7. *You stated that tezacaftor* (b) (4) *and particle size (PSD) were not identified to be CQAs for tezacaftor* (b) (4)*. Variation in* (b) (4) *and PSD has a potential*

to impact (b) (4) *. Provide data to support your rationale for designating material properties of tezacaftor* (b) (4) *as non-critical*

3.0 ATTACHMENTS AND HANDOUTS

23 Page(s) have 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.

/s/

BAMIDELE F AISIDA
05/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108105

MEETING MINUTES

Vertex Pharmaceuticals Inc.
Attention: Carly Evans
Director, Regulatory Affairs CMC
50 Northern Avenue
Boston, MA 02210

Dear Ms. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-661.

We also refer to the meeting between representatives of your firm and the FDA on September 14, 2016. The purpose of the meeting was to elicit Agency feedback on Continuous Process Verification (CPV), an alternative approach to validation Vertex is considering for implementation..

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Florence Aisida, Regulatory Project Manager, at (240) 402-2691.

Sincerely,

{See appended electronic signature page}

Derek Smith, Ph.D.
Branch Chief, Branch II (Acting)
Division of Inspectional Assessment
Office of Pharmaceutical Quality
Center for Drug Evaluation and ResearchEnclosure:

Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	CMC
Meeting Date and Time:	September 14, 2016, 12:00 PM – 1:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 108105
Product Name:	VX-661
Indication:	Treatment of Cystic Fibrosis
Sponsor/Applicant Name:	Vertex Pharmaceuticals Inc.
Meeting Chair:	Derek Smith, Ph.D.
Meeting Recorder:	Florence Aisida

FDA ATTENDEES

Eric Duffy, PhD., Division Director, New Drug Products
Rapti D. Madurawe, Ph.D., Acting Division Director, Process Assessment
Sharmista Chatterjee, PhD., Acting Division Director, Process Assessment
Sau (Larry) Lee, Ph.D., Deputy Director (Acting), ETT Chair, Office of Testing and Research
Craig Bertha, Ph.D., Acting Quality Assessment Lead, New Drug Products
Derek Smith, Ph.D., Acting Branch Chief, Inspectional Assessment
Zhigang Sun, Ph.D., Acting Branch Chief, Process Assessment
Yong Hu, Ph.D., Acting Quality Assessment Lead, Process Assessment
Christina Capacci-Daniel, Ph.D., Acting Quality Assessment Lead, Inspectional Assessment
Florence Aisida, Pharm D., BCPS, Regulatory Business Project Manager
Steven Kinsley, Ph.D., Regulatory Business Project Manager
Celia N. Cruz, Ph.D., Acting Division Director, ETT Representative

SPONSOR ATTENDEES

Amy Walia, Director, Regulatory Affairs CMC
Carly Evans, Director, Regulatory Affairs CMC
Stephanie Krogmeier, Ph.D., Senior Director, Regulatory Affairs CMC
Eleni Dokou, Ph.D., Senior Director, Formulation Development
Hayden Thomas, Ph.D., Vice President, Process Development
Kelly Swinney, Ph.D., Senior Director, Analytical Development
Kelly Tolton, Senior Director, Technical Operations

Thomas Gandek, Ph.D., Vice President, Technical Operations
Geny Doss, Vice President, Quality Assurance
James Currin, Associate Director, Quality Assurance
Robert Castellucci, Vice President, Quality Assurance

1.0 BACKGROUND

Vertex Pharmaceuticals, Inc. is currently conducting pivotal Phase 3 studies with VX-661/ivacaftor fixed dose combination (FDC) tablets and developing the FDC as a continuous manufacturing process under a Quality by Design (QbD). The purpose of the Type B meeting is to elicit Agency feedback on an alternative validation approach Vertex is considering for implementation. The Continuous Process Verification (CPV) approach is intended to be implemented for the VX-661/ ivacaftor FDC tablet currently under development with an anticipated filing timeline in the second half of 2017.

FDA sent Preliminary Comments to Vertex on September 9, 2016.

2. DISCUSSION

Question 1: **Does the Agency agree that the Vertex approach to CPV is consistent with the Agency's Validation expectations, including:**

FDA Response: *Given the innovative nature of the proposed VX-661/Ivacaftor continuous manufacturing process, it is appropriate to discuss your general approach to Process Validation,* (b) (4) *However, we remind you the FDA does not approve process validation protocols or the number of specific batches used in process performance qualification studies. The actual protocols, acceptance criteria, and study outcomes (as applicable) will be evaluated during an on-site inspection of your manufacturing facilities. Likewise, the product and manufacturing process design and control strategy will be evaluated during the NDA review cycle. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product and remains in a validated state.*

a) (b) (4) .

FDA Response: *We remind you that* (b) (4) *For a continuous process, a thorough process understanding is critical for establishing material traceability, designing an adequate control strategy, and assessing remaining sources of manufacturing variability or risks and the potential impact on critical quality attributes. Particularly for*

continuous manufacturing processes, adequate design and performance qualification of equipment and automated control systems which operate the process in real-time, is essential.

Your briefing package notes that you will leverage prior knowledge from your already approved continuous manufacturing process and control strategy for VX-809/VX-770. However, we would like to point out a few potential major differences between your two manufacturing processes:

- (b) (4)
-
-

The FDA encourages a science-based, lifecycle approach to process validation and recommends the use of process design and development studies to build robustness into the manufacturing process. (b) (4)

[redacted] *the documents listed in Table 4 of your Background Material file (e.g. PQC, VMP) lack* [redacted] *protocol details. A definitive response on the acceptability of the proposed* [redacted] *cannot be provided; the* [redacted] *protocol and results will be evaluated on-site during an inspection.*

Additional Considerations:

For the [redacted]*, you are encouraged to consider acceptance criteria suitable to a continuous process that can be used to assess robustness.* [redacted]

[redacted]

[redacted]

b) [redacted]

FDA Response: [redacted]

(b) (4)

Lastly, your briefing document references 21 CFR 820.75 for guidance on Process Validation. This regulation pertains to medical devices. While informative, it is not directly applicable to the proposed manufacturing process. For information on process validation for pharmaceuticals, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Additionally, principles in ICH Q10 related to process improvement are pertinent to this discussion of continued process verification. "Guidance for Industry, Q10 Pharmaceutical Quality System" is provided at the following link:

http://www.fda.gov/downloads/Drugs/Guidances/ucm073517.pdf

Meeting Discussion:

Vertex presented the slides attached to the end of this document. During the presentation, FDA and Vertex addressed some clarification comments on process and control strategy development, which was noted to follow closely the QbD methodology used for Orkambi. Vertex clarified that, prior to the manufacture of the proposed (b) (4) validation batch, additional development and registration batches, some of which are of commercial scale in terms of batch size/process run time would be manufactured (b) (4). At the conclusion of the presentation, Vertex asked what were the most import factors/heightened concerns that the FDA had for batch size, process variability and process monitoring, especially as applied to facility inspections. FDA stated that the major areas are outlined in the original

response document in response to the use of (b) (4) batch. FDA also stated that operation at the commercial scale batch size/process run time may uncover risks or process variability that were not apparent at smaller scales and these should be mitigated.

(b) (4)

3.0 ATTACHMENTS AND HANDOUTS

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/s/

DEREK S SMITH
10/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108105

MEETING MINUTES

Vertex Pharmaceuticals
130 Waverly Street
Cambridge, MA 02139
Attention: Alissa Minkoff, MS
Regulatory Affairs

Dear Ms. Minkoff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-661.

We also refer to the meeting between representatives of your firm and the FDA on November 5, 2014. The purpose of the meeting was to discuss phase 3 clinical development plan for VX-661 in combination with ivacaftor.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Angela Ramsey, RN, MSN, MPH
Senior Program Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: November 5, 2014
Meeting Location: FDA White Oak, Building 22, Conference Room 1419

Application Number: 108105
Product Name: VX-661 in combination with ivacaftor
Indication: Cystic Fibrosis
Sponsor/Applicant Name: Vertex Pharmaceuticals

Meeting Chair: Badrul A. Chowdhury, MD, Ph.D
Meeting Recorder: Angela Ramsey, RN, MSN, MPH

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lim, Robert, M.D., Clinical Reviewer
Anthony Durmowicz, M.D., Clinical Team Leader
Lawrence Leshin, Ph.D., Nonclinical Reviewer
Marcie Wood, Ph.D., Non-Clinical Team Leader
Jianmeng Chen, Ph.D., Clinical Pharmacology Reviewer
Satjit Brar, Ph.D., Clinical Pharmacology Team Leader
David Petullo, Ph.D., Statistical Team Leader
Craig Bertha, Ph.D., CMC Lead

SPONSOR ATTENDEES

Jeff Chodakewitz, MD, Sr. Vice President, GMDA and Chief Medical Officer
Patricia Hurter, PhD, Sr. Vice President, CMC and Pre-clinical Development
Rick Lilley, PhD, Sr. Vice President, Regulatory Affairs
Dennis Dean, PhD, Sr. Vice President, Preclinical Development
Charlotte McKee, MD, Vice President, Clinical Development
Antoinette Paone, MS, MBA Vice President, Global Regulatory Affairs
Julie Lekstrom Himes, MD, Sr. Medical Director, Clinical Development
David Brewster, PhD Vice President, Nonclinical Development
Sameer Upadhyay, MD, Sr. Director, Global Patient Safety
Jinshan Shen, PhD, Director, Clinical Pharmacology
Fred Van Goor, PhD Sr. Research Fellow, Biology
Mei-Hsiu Ling, PhD, Director, Biostatistics

Kaity Posada, PharmD, Director, Global Regulatory Affairs
James Sullivan, PhD, Director, Clinical Biomarkers
Alissa Minkoff, MS, Sr. Associate, Global Regulatory Affairs

BACKGROUND
Vertex submitted a Type B meeting request dated, August 28, 2014 to discuss phase 3 clinical development plans for VX-661 in combination with ivacaftor in the treatment of Cystic Fibrosis. Vertex submitted background material dated, October 6, 2014. Upon review of the material, the Division responded via secure email on November 3, 2014. Vertex requested to continue with the face-to-face meeting to clarify responses in the Introductory Comments and responses to questions 1, 2 and 5. Vertex provided handouts outlining discussion points (see attachment).

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant responses. The sponsor's questions are in ***bold italics***; the Division responses are in *italics*; and discussion is in normal font.

DISCUSSION
FDA Introductory Comment:
Conceptually, we agree that a VX-661/ivacaftor (iva) development program could eventually support an indication for treatment of CF in patients with a F508del mutation in the CFTR gene on at least 1 allele by studying separate populations of CF patients heterozygous for F508del. We have the following general comments regarding the overall program:

- *We recommend that you include an ivacaftor monotherapy comparator arm in your proposed clinical trials.*
- *You are currently developing 2 CFTR "corrector/potentiator" combination products for the same indication. If approved and you plan to market both products, you will need to provide comparative safety data. As such, we recommend that you include a lumacaftor/iva treatment arm within Study 106.*
- *As your clinical trials are powered to detect small effects in FEV_1, a modest improvement in FEV_1 may be found statistically significant. If this occurs, to clearly demonstrate efficacy, it will be important that the studies also suggest benefit on an additional clinically meaningful endpoints (e.g., exacerbation rate, CFQ-R respiratory domain score, BMI, etc.).*
- *In the testing hierarchy scheme for your secondary endpoints, we recommend that absolute change in CFQ-R respiratory domain score be tested before absolute change from baseline in BMI.*
- *Clarify and justify the differences in the effect sizes at which the four proposed phase 3 clinical trials are powered. For example, it is unclear why Study 109 is powered to detect a larger difference, versus an active comparator, than Studies 106, 107, and 108, for which the control group is receiving placebo.*
- *Clarify the need for the variety of exceptions to blinding (Protocols Section 8.3.1). In particular, clarify that the vendor preparing analyses for the IDMC is independent and explain what is meant by the reference to an "unblinded Vertex team"*

Discussion:
The Division questioned the rationale for developing VX-661/ivacaftor in light of the recent NDA submission for lumacaftor/ivacaftor (lum/iva). Vertex responded that they believed that VX-661/ivacaftor may benefit a broader population as the treatment effect appear larger compared to lum/iva, there was no administration associated bronchospasm, and VX-661 did not appear to have the same drug-drug interactions as lumacaftor. The Division inquired as to Vertex's plans were both combinations to be approved and if specifically lum/iva would be withdrawn if VX-661/iva was ultimately approved. Vertex responded that it was premature to answer that question.

Vertex discussed the overall goals of the Phase 3 program (referenced slide 4) and provided rationale for the proposed effect sizes in the proposed trials (slide 5). Vertex also stated that the ability for study 106 to detect such small change in FEV1 was because the study was also powered to detect a 40% reduction in exacerbations.

Vertex then provided their rationale for not including an ivacaftor monotherapy comparator arm (Slide 6). They stated that based on *in vitro* data and the results of the 16-week study in *F508del* homozygous patients (study VX08-770-104), they firmly believed that ivacaftor is not effective in *F508del* homozygous patients. They also referred to the limitations of use in the approved label. For these reasons, they believed that placebo comparison was sufficient in studies 106 and 107. The Division disagreed, stating that in study 106, powering of the study was such that a treatment difference versus placebo of just 1.5% in terms of percent predicted FEV1 (ppFEV1) could be statistically significant, and noted that such an effect size is numerically similar to the observed ppFEV1 difference seen in VX08-770-104 (1.7%). As such, if study 106 shows a small but statistically significant ppFEV1 effect, it will be difficult to conclude that VX-661 contributes to the effect of VX-661/ivacaftor. Consideration of the clinical relevance of the size of the observed effect on FEV1, a surrogate endpoint, will be important.

The Division also noted that in the lumacaftor/ivacaftor program, the effect on FEV1 was similar in magnitude to that seen in study VX08-770-104, and that, based on a preliminary review, an effect on exacerbation rate was observed. The Division also noted that in study VX08-770-104, although there were very few exacerbations observed, there was a trend toward exacerbation reduction with ivacaftor. As such, had study VX08-770-104 been larger or specifically powered for exacerbation, it is possible that the results could have been similar to the lumacaftor/ivacaftor trials.

The Division concluded by stating that studies 106 and 107 should include an ivacaftor comparator arm and that the ivacaftor comparator arm can be added in lieu of the placebo arm. Vertex stated that they would discuss internally the feasibility of including an ivacaftor monotherapy arm.

Question 1:
Does the Agency agree with the populations defined for the Phase 3 studies?

FDA Response:
We have the following comments regarding the definition of the study populations and study design:

Study 106 (F508del homozygous)

- *We note that the study treatment duration is 24 weeks. While adequate to assess lung function (FEV_1) and change in respiratory symptoms (CFQ-R, respiratory domain), 24 weeks may not be of long enough to assess a reduction in exacerbations.*
- *The proposed design is based on the assumption that the study's 24-week treatment period will be complete prior to the availability of the lumacaftor/iva combination product for treatment of CF patients homozygous for the F508del mutation (if approved).*

Discussion (Slide 10 & 11):
The Division voiced the concern that 24 weeks may not be sufficient to demonstrate an effect on exacerbation. The Division reiterated the need for lumacaftor/ivacaftor treatment arm to provide a source of comparative intra-study safety data. The Division also stated that such data would be needed either pre- or post-marketing. Vertex proposed re-randomizing a subset of patients at the end of the 24-week treatment period to lumacaftor/ivacaftor treatment to allow for a safety comparison. The Division agreed that that approach was conceptually reasonable. The Division also voiced a concern that if lumacaftor/ivacaftor was to be approved while study 106 was ongoing, there may be an increase in patient discontinuations in lieu of an approved therapy. The Division stated that the expectation was that missing data/patient dropout in VX-661/ivacaftor trials would be very minimal and similar to that seen in the lumacaftor/ivacaftor and ivacaftor programs.

Study 107 (F508del/NR allele)

- *Approval of VX-661/iva for the F508del/NR subpopulation will be based on positive results in this study as well as positive results in Study 106 (F508del homozygous population).*
- *Consider a separate study or separate analysis for the subpopulation of CF patients who possess a Class 1 mutation (no functional CFTR is produced such as G542X) in the second allele. This would be in contrast, for example, to those with a Class II mutation similar to the F508del in the second allele where full length CFTR is produced but there is a processing or trafficking defect.*
- *Justify how a Class IV mutation, generally considered as having a conductance defect, would be predicted to not respond to ivacaftor or the VX-661/iva combination and, therefore, be included as a "not responsive" mutation.*
- *We note that the treatment period for the study is 12 weeks. This shorter treatment period effectively limits the evaluable of key endpoints for the study primarily to FEV_1 and CFQ-R revised.*
- *We do not necessarily agree with your definition of the mutations included in this study as those who are "nonresponsive" to ivacaftor. For example, justify the inclusion of any CF patient with pancreatic sufficiency (defined by lack of use of supplemental pancreatic enzymes) and the ability for in vitro testing or a sweat chloride threshold > 86 mmol/L predicts lack of clinical response to ivacaftor.*

Discussion (Slides 13-20):
Vertex agreed to perform a sensitivity analysis for patients with class I mutations. The Division commented that we did not necessarily agree with how non-responsive was defined. The Division pointed out that it is unclear how well the *in vitro* responsiveness/non-responsiveness correlates with the clinical characteristics of a given mutation. Because of this lack of concordance the Division noted that grouping mutations based on these criteria could potentially be problematic.

Study 108 (F508del/RF allele)

- *The ability for this to support approval for the F508del/RF population will be dependent on an approval action for ivacaftor as a treatment for CF patients who have a R117H mutation in the CFTR.*
- *Similar to Study 107, the potential basis for approval for the F508del/residual function population is a short 8-week treatment period which effectively limits the evaluable key endpoints for the study primarily to FEV_1 and CFQ-R revised.*
- *As mentioned above, you will need to demonstrate the ability for in vitro testing or a sweat chloride threshold ≤ 86 mmol/L to predict clinical residual function in the CFTR. In the same light, explain by what other clinical parameters in a patient who is pancreatic insufficient could be used to determine "residual function" in the CFTR.*
- *We note that the R117H sub-population, a known mutation associated with maintenance of CFTR residual function, is excluded from the F508del/RF population in this study. While ethical considerations may preclude giving placebo to patients with a R117H mutation in the CFTR, if ivacaftor is approved for treatment of patients with a R117H mutation in the future, we recommend inclusion of an R117H mutation active treatment subgroup in this study as a benchmark.*

Discussion (Slides 21-24):
The Division noted that including the R117H mutation in this trial would not be feasible if ivacaftor was approved for treatment of cystic fibrosis patients with that mutation.

Study 109 (F508del/responsive allele)

- *Note that the G970R mutation has not been clinically demonstrated to be ivacaftor-responsive.*
- *Given that all patients will be receiving an efficacious treatment during the run-in period, an 8-week treatment period may not be sufficient to determine if the VX-661/iva combination demonstrates efficacy in any parameter other than FEV_1 and CFQ-R revised. Additionally, given for the proposed population that FEV_1 is known to increase 10-12% of predicted in response to ivacaftor, demonstrating a further statistically significant and clinically meaningful improvement in FEV_1 may be difficult.*

Discussion (Slides 25-26):
The Division reiterated that the G970R mutation has not been clinically demonstrated to be ivacaftor responsive. As such, inclusion of G970R in study 109 was potentially problematic. (b) (4)

Question 2:

Does the Agency agree with the proposed Phase 3 clinical study designs

- ***a. Does the Agency agree with the overall elements for the proposed Phase 3 clinical studies?***
- ***b. Does the Agency agree with the clinical study design, (primary endpoint, secondary endpoints, safety assessments, analysis plan) and duration for the pivotal study in F508del homozygous subjects? (Study 106)***
- ***c. Does the Agency agree with the clinical study design (primary endpoint, secondary endpoints, safety assessments, analysis plan) and duration for the pivotal study in F508del-CFTR heterozygous subjects with an ivacaftor and VX-661 non-responsive mutation on the second allele (F508del/NR)? (Study 107)***
- ***d. Does the Agency agree with the clinical study design (primary endpoint, secondary endpoints, safety assessments, analysis plan) and duration for the pivotal study in F508del-CFTR heterozygous subjects with a residual function mutation that is potentially ivacaftor responsive on the second allele (F508del/RF)? (Study 108)***
- ***e. Does the Agency agree with the clinical study design (primary endpoint, secondary endpoints, safety assessments, analysis plan) and duration for the pivotal study in F508del-CFTR heterozygous subjects with a clinically proven ivacaftor-responsive mutation with a gating defect on the second allele (F508del/gating)? (Study 109)***

FDA Response 2a-e:

See introductory comments and response to question 1.

Discussion:

No discussion occurred.

Question 3:

Does the Agency agree that if all 4 clinical studies are successful this would support an indication for the treatment of CF in subjects aged 12 years and older with an F508del-CFTR mutation on at least 1 allele? Additionally, does the Agency agree that approvability of an indication in a subset of this population is achievable based on the success of 1 or more of the Phase 3 studies?

FDA Response:

If all four trials clearly demonstrate a clinically meaningful treatment effect in the studied populations in all of the genotypes studied, these trials would potentially be supportive of the proposed indication (F508del heterozygotes). If only 1, 2, or 3 of the 4 trials clearly demonstrate a clinically meaningful treatment effect, then it is possible that the results would be supportive of an indication in the studied population(s); however, we do have some concerns/comments regarding your proposed studies/populations (see introductory comments and response to question 1).

Discussion:

No discussion occurred.

Question 4:
Does the Agency agree with the proposed safety database to support an initial NDA filing for VX-661/ivacaftor combination therapy?

FDA response:
The proposed safety database for 1-year is relatively small for a chronically administered drug. However, as this is an orphan disease, it may be sufficient assuming no safety concerns are identified in the overall program and no safety signal is seen in Study 103.

Discussion:
No discussion occurred.

Question 5:
Does the Agency agree that the proposed clinical pharmacology studies are adequate to support planned Phase 3 studies and registration of VX-661 in combination with ivacaftor for the intended indications?

FDA Response:
In general, we agree with your strategy to address drug-drug interaction and special population studies for the VX661 clinical pharmacology program. However, we note that you do not have any PK information to support the FDC formulation of 100 mg VX661/150mg VX770 for the phase 3studies, and there is no data to bridge the FDC (100/150 mg) to the separate tablets used in phase 2 study 101. Note that this data will be necessary for NDA submission (and preferably prior to initiation of phase 3 trials).

Also, we note that the exposure of ivacaftor increased by 31% in presence of VX661 (study 017), and that VX661 exposure may increase in presence of ivacaftor (study 101). Please address these issues in your VX-661/iva development program and in any subsequent NDA submission to clarify that any efficacy observed for the VX-661/iva combination product is not due to increased systemic exposure of either of the two drugs.

Discussion (Slides 28-29):
Regarding the FDC (100/150 mg) PK information (slide 28), the Division acknowledged that the proposed studies would be sufficient to support NDA submission, (b) (4) . The Division also noted the potential risk to proceed to phase III studies without any human PK data with the proposed to-be-marketed FDC, and left this as sponsor's own decision. The Division commented that there is no FDC in-vitro data and requests that Vertex submit in-vitro data for FDC formulation before starting Phase 3.

Regarding the potential DDI between ivacaftor and VX661 (slide 29), the Division noted that the PK data is limited and the dose ranging study for ivacaftor was performed in only one mutation. The Division suggested that the sponsor should provide sufficient justification regarding the combination rule, to demonstrate that the efficacy is not due to increased exposure of ivacaftor or VX661. The sponsor may explore exposure-response analysis, in-vitro pharmacology data, and

phase III data to demonstrate the efficacy contribution of VX-661 and ivacaftor in the combination.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ATTACHMENTS AND HANDOUTS

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/s/

ANGELA H RAMSEY
12/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108105

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA 02210

Attention: Adel Al-Shaikh, MSc, RAC
Manager, Regulatory Affairs

Dear Mr. Al-Shaikh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-661.

We also refer to your December 3, 2013, request for Breakthrough Therapy designation. We have reviewed your request and have determined that VX-661 in combination with ivacaftor meets the criteria for Breakthrough Therapy designation for the treatment of Cystic Fibrosis patients who are homozygous for the *F508del* mutation in the *CFTR*. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of VX-661 for Cystic Fibrosis, including providing advice on generating evidence needed to support approval of the drug in an efficient manner. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*[1] for procedures on requesting a meeting.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

If you have any questions, contact Angela Ramsey, Senior Program Management Officer, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.,
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

LYDIA I GILBERT MCCLAIN
01/28/2014
Acting Division Director for Dr. Badrul Chowdhury

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210491

LATE-CYCLE MEETING MINUTES

Vertex Pharmaceuticals Inc.
50 Northern Ave.
Boston, MA 02210

Attention: Charlotte Heyman, MSc
Regulatory Senior Manager, Global Regulatory Affairs

Dear Ms. Heyman:

Please refer to your New Drug Application (NDA) dated June 28, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for tezacaftor/ivacaftor tablet.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 19, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Lee, Regulatory Project Manager at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Anthony Durmowicz, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 19, 2017 at 2:00 PM
Meeting Location: via Teleconference

Application Number: NDA 210491
Product Name: Tezacaftor/Ivacaftor
Applicant Name: Vertex Pharmaceuticals

Meeting Chair: Anthony Durmowicz, MD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Mary Thanh Hai, MD, Deputy Director, Office of Drug Evaluation II
Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Anthony Durmowicz, MD, Clinical Team Leader, DPARP
Stacy Chin, MD, Clinical Reviewer, DPARP
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Christina Capacci-Daniel, PhD, Consumer Safety Officer, Inspectional Assessment Branch II
Xiaobin Shen, PhD, Chemist, New Drug Products Branch IV
Jessica Lee, PharmD, Senior Regulatory Project Manager, DPARP

APPLICANT ATTENDEES

Nia Tatsis, Ph.D: Sr. VP Global Regulatory Affairs
Lynette Hopkinson: VP Global Regulatory Affairs
Gemma Pilkington: Director, Global Regulatory Affairs
Charlotte Heyman: Sr. Manager, Global Regulatory Affairs
Hayley Parker: Sr. Director, Global Regulatory Affairs (Labeling)
Reshma Kewalramani, MD: Sr. VP R&D Management
Julie Lekstrom, MD: Senior Medical Director, Clinical Development
Christopher Simard, MD: Senior Medical Director, Global Patient Safety

Varun Garg, PhD: Senior Director, Clinical Pharmacology
Amit Sachdev: Executive VP, Chief Regulatory Officer
Jeff Chodakewitz, MD: Executive VP, Chief Medical Officer

1.0 BACKGROUND

NDA 210491 was submitted on June 28, 2017 for tezacaftor/ivacaftor.

Proposed indication: Cystic Fibrosis

PDUFA goal date: February 28, 2018

FDA issued a Background Package in preparation for this meeting on December 11, 2017.

2.0 DISCUSSION

1. Introductory Comments

Discussion:

No substantive review issues have been identified since the last interaction at the Mid-Cycle communication on November 2, 2017.

2. Discussion of Minor Review Issues

Discussion:

- Discussion of labeling is a minor issue that is outstanding and the label will (b) (4) . Labeling comments and edits will be provided to Vertex by December 29, 2017.

- No major issues have been identified for the carton/container labels.

3. Discussion of Upcoming Advisory Committee Meeting

Discussion:

No Advisory Committee Meeting has been planned for this application.

4. Postmarketing Requirements/Postmarketing Commitments

Discussion:

No PMR/PMC have been identified at this time.

5. Major Labeling Issues

Discussion:

Given the [redacted] (b) (4) no other major labeling issues have been identified.

6. Review Plans

Discussion:

The action on the Pediatric Rare Disease Voucher request will be provided to Vertex on the day of the NDA action.

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL); therefore, this meeting did not address the final regulatory decision for the application.

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/s/

ANTHONY G DURMOWICZ
01/16/2018