

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207925Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207925

SUPPL #

HFD # 570

Trade Name Kalydeco granules

Generic Name ivacaftor

Applicant Name Vertex Pharmaceuticals

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 203188

Kalydeco (ivacaftor) tablet

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 108

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Study 108 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study 108

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 74633	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Angela Ramsey
Title: Senior Program Management Officer
Date: March 17, 2015

Name of Office/Division Director signing form: Badrul A. Chowdhury, MD, PhD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
03/17/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207925 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Kalydeco Established/Proper Name: ivacaftor Dosage Form: 50 and 75 mg granules		Applicant: Vertex Pharmaceuticals Agent for Applicant (if applicable):
RPM: Ramsey		Division: Pulmonary, Allergy, and Rheumatology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: </p> <p style="margin-left: 20px;"><i>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.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>March 17, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

- | | |
|--|---|
| <input checked="" type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) March 17, 2015
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> • Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (indicate date(s)) • Review(s) (indicate date(s)) 	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 12/19/14 DMEPA: <input type="checkbox"/> None 2/18/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 2/17/15 OPDP: <input type="checkbox"/> None 2/25/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	12/19/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>NA</u> If PeRC review not necessary, explain: <u>Orphan Designation</u> 	
❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	3/12/15; 3/6/15; 2/13/15; 12/10/14; 11/26/14; 11/06/14; 9/19/14
❖ 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)	2/12/15; 1/9/15; 1/2/15; 12/16/14
❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 12/12/12 <input type="checkbox"/> N/A 12/19/14 <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/17/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/28/15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review 2/19/15; 11/19/14 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	review dated 2/19/15 pg 34
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 1/6/15; 12/17/14
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/24/15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/20/15; 11/26/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 2/19/15
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2/2/15; 10/21/14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 2/11/15
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Biopharm 1/7/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2/2/15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 2/18/15 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input type="checkbox"/> Done

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
03/17/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: March 12, 2015

To: Guilin Huang, , MBA, RAC, Manager Regulatory Affairs	From: Angela Ramsey Senior Program Management Officer
Company: Vertex Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 857-263-4606	Fax number: 301-796-9728
Phone number: 617-961-1707	Phone number: 301-796-2284

Subject: NDA 207925 (Kalydeco granules) submission dated, September 17, 2014 Labeling fax

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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NDA 207925

Your NDA submission dated, September 17, 2014 for Kalydeco granules is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and patient leaflet. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. In addition we also have the following comments:

1. We acknowledge and agree with your intent to relocate the statement 'Mfd for...' to the bottom of the label postmarketing. Note that, similar to the prescribing information, the name of the drug/dosage form on the carton and container should read "oral granules".
2. Note that, consistent with our current focus on good labeling practices, the Kalydeco label has been reviewed by an FDA label format expert. Please update the label format based on tracked change comments included in the attached FDA-proposed label.
3. Note that with the oral granule formulation being available, there will be an age appropriate dosage form that can be given to child (b) (4). This raises a real safety concern, especially for infants whose liver metabolic function may not yet be fully developed where there may be the potential for very high drug exposure. Include in the label appropriate language to help address this issue.

Submit revised labeling incorporating changes shown in the attached marked up labeling for the package insert and patient information by noon March 16, 2015.

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

Drafted by: Ramsey/March 12, 2015
Initialed by: Barnes/March 12, 2015; Durmowicz/March 12, 2015
Finalized: Ramsey/ March 12, 2015

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

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/s/

ANGELA H RAMSEY
03/12/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: March 6, 2015

To: Guilin Huang, , MBA, RAC, Manager Regulatory Affairs	From: Angela Ramsey Senior Program Management Officer
Company: Vertex Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 857-263-4606	Fax number: 301-796-9728
Phone number: 617-961-1707	Phone number: 301-796-2284

Subject: NDA 207925 (Kalydeco granules) submission dated, September 17, 2014 Labeling fax

Total no. of pages including cover:

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NDA 207925

Your NDA submission dated, September 17, 2014 for Kalydeco granules is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI) and patient leaflet. The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

A. Granules Container Label

Relocate the statement 'Mfd for...' to the bottom of the label to decrease clutter and increase readability.

B. Prescribing Information

1. The symbol '<' and '≥' were utilized in the labeling to represent "less than" and "greater than or equal to". These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. As part of a national campaign to decrease the use of dangerous symbols, the FDA agreed to not use such error-prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore we replaced the reference symbols with words.
2. Note that "Cataracts" should be included in the Warnings and Precautions section of the Highlights.
3.  (b) (4)

Submit revised labeling incorporating changes shown in the attached marked up labeling for the package insert and patient information by March 10, 2015.

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

Drafted by: Ramsey/March 6, 2015
Initialed by: Barnes/March 6, 2015; Durmowicz/March 6, 2015
Finalized: Ramsey/ March 6, 2015

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/s/

ANGELA H RAMSEY
03/06/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207925

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

ATTENTION: Guilin Huang, MBA, RAC
Manager, Global Regulatory Affairs

Dear Mr. Huang:

Please refer to your New Drug Application (NDA) dated and received September 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ivacaftor Granules, 50 mg and 75 mg.

We also refer to your correspondence, dated and received December 17, 2014, requesting review of your proposed proprietary name, Kalydeco. We have completed our review of the proposed proprietary name, Kalydeco and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 17, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Angela Ramsey, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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/

TODD D BRIDGES
03/05/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: February 13, 2015

To: Guilin Huang, , MBA, RAC, Manager Regulatory Affairs	From: Angela Ramsey Senior Program Management Officer
Company: Vertex Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 857-263-4606	Fax number: 301-796-9728
Phone number: 617-961-1707	Phone number: 301-796-2284

Subject: NDA 207925 (Kalydeco granules) submission dated, September 17, 2014 Labeling fax

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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NDA 207925

Your supplemental NDA submission dated, September 17, 2014 for Kalydeco is currently under review. The enclosed label contains the Division's edits to your propose package insert (PI). The Division's proposed insertions are underlined; deletions are in strike-outs. These comments are not all-inclusive and we may have additional comments as we continue our review. We also have the following comments:

1. Note that in the Highlights, Warnings and Precautions, and Adverse Reactions, and Patient Counseling we have recommended extending the labeling comment regarding the potential increased risk of transaminase elevations in patients 2-5 years of age who had abnormal transaminases at baseline to the entire patient population. This recommendation is based on a similar observation seen in the G551D program [i.e., transaminase elevations were more common in ivacaftor treated patients with a history of transaminase elevations compared to those without; Summary of Clinical Safety table 27 and 28 (pg 69 and 70) submitted 10/18/11]. While the numbers overall are small, the consistency across age groups and clinical judgment suggest the association may be real. Feel free to propose alternate wording.
2. Additional potential labeling edits or comments regarding the ciprofloxacin DDI study will be forthcoming in the next label iteration.

Submit revised labeling incorporating changes shown in the attached marked up labeling for the package insert and patient information by February 19, 2015.

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

Drafted by: Ramsey/February 13, 2015
Initialed by: Barnes/February 13, 2015; Durmowicz/February 13, 2015
Finalized: Ramsey/ February 13, 2015

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/s/

ANGELA H RAMSEY
02/13/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: December 19, 2014

Application Number: NDA 207925

Product Name: Kalydeco (ivacaftor) granules

Sponsor/Applicant Name: Vertex Pharmaceuticals

Subject: Mid-Cycle Communication

FDA Participants : CDR. Angela Ramsey RN, MSN, MPH
Senior Program Management Officer

Sponsor/Applicant Participants Guilin Huang, MBA, RAC
Manager, Regulatory Affairs

CDR. Angela Ramsey provided Guilin Huang a Mid-Cycle review update for Kalydeco (ivacaftor) granules in the treatment of CF patients 2-6 years old with mutations in the CFTR gene. CDR Ramsey commented that the reviews are ongoing and there are no outstanding issues at the present time. Ms. Huang acknowledged the review update and will inform the Vertex team of the update.

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/s/

ANGELA H RAMSEY
02/06/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: December 10, 2014

To: Guilin Huang, MBA, RAC Manager Global Regulatory Affairs	From: Angela Ramsey Senior Program Management Officer
Company: Vertex Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 617-341-6803	Fax number: 301-796-9728
Phone number: 617-961-0003	Phone number: 301-796-2284

Subject: NDA 207925 (ivacaftor) submission dated, September 17, 2014

Total no. of pages including cover:

Comments:

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received this document in error, please notify us immediately by telephone at
(301) 827-1050. Thank you.**

NDA 207925

Your NDA dated, September 17, 2014 for ivacaftor granules is currently under review.

1. Reference is made to Report K199 for pediatric population pharmacokinetics and we have the following requests for information:

Model predicted exposure in the targeted age group is used to justify the proposed doses. Submit the NONMEM dataset and control stream used to predict the exposures in various age groups (figures 49 and 50 in the k199 report). Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files submitted as ASCII text files (eg, myfile_ctl.txt, myfile_out.txt).

2. Submit the pharmacokinetics dataset (or PC for data tabulation dataset SDTM) for study VX12-770-015. Data files should be submitted as SAS transport files (eg, Data1.xpt).

To facilitate review, submit response by December 15th 2014 to angela.ramsey@fda.hhs.gov and submit officially to the NDA.

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

Drafted by: Ramsey/December 10, 2014

Initialed by: Barnes/December 10, 2014; Rekić/December 9, 2014; Zhao/December 9, 2014

Finalized: Ramsey/ December 10, 2014

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/s/

ANGELA H RAMSEY
12/10/2014



NDA 207925

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA 02210

Attention: Guilin Huang, MBA, RAC
Manager Regulatory Affairs

Dear Ms. Huang:

Please refer to your New Drug Application (NDA) dated September 17, 2014, received submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Kalydeco (ivacaftor) granules.

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 March 17, 2015.

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 24, 2015.

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

Clinical

1. Efficacy for the 2-5 year old population is extrapolated from the existing data in the older population. (b) (4)

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.

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](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), 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 product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call 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

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/s/

BADRUL A CHOWDHURY
11/26/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

Date: November 6, 2014

To: Alissa Minkoff, MS Global Regulatory Affairs	From: Angela Ramsey Senior Program Management Officer
Company: Vertex Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: 617-341-6803	Fax number: 301-796-9728
Phone number: 617-961-0003	Phone number: 301-796-2284

Subject: NDA 207925 (ivacaftor) submission dated, September 17, 2014

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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NDA 207925

Your NDA dated, September 17, 2014 for ivacaftor granules is currently under review. Reference is made to Report K199 for pediatric population pharmacokinetics and we have the following requests for information:

1. Provide a prediction corrected visual predictive check (VPC) as well as age stratified VPCs for model 1007 using time after dose (TAD, 0 to 24 h) as the independent variable. Age groups for stratification should be: 2-5 years 14 kg and below, 2-5 years above 14 kg, 6-11 years, 12-17 years, and adults. In addition to the VPCs, provide an absolute individual weighted residual (|IWRES|) versus individual prediction (IPRED) plot. Provide justification if you choose to use other type of diagnostic plots.
2. The allometric exponents for the current model are fixed to $\frac{3}{4}$ and 1 for clearance and volume terms, respectively. Test a model with the allometric exponents estimated and compare the simulated Cmin's at steady state for all the age groups between these two models. Of note, the new model should also be evaluated with diagnostic plots suggested above and any additional diagnostics you find suitable.

Conduct the additional analyses including Datasets, NONMEM control streams, and scripts used to generate analyses and plots. Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files should be submitted as ASCII text files (eg, myfile_ctl.txt, myfile_out.txt).

To facilitate review, submit your report by November 12th 2014 to angela.ramsey@fda.hhs.gov and submit officially to the NDA.

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

Drafted by: Ramsey/October 28, 2014
Initialed by: Barnes/October 28, 2014; Zhao/October 28, 2014
Finalized: Ramsey/ November 6, 2014

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/s/

ANGELA H RAMSEY
11/06/2014



NDA 207925

NDA ACKNOWLEDGMENT

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA 02210

Attention: Alissa Minkoff, MS
Senior Associate Global 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: ivacaftor granules

Date of Application: September 17, 2014

Date of Receipt: September 17, 2014

Our Reference Number: NDA 207925

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 November 16, 2014, 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).

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, electronic or paper, including those sent by overnight mail or courier, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. 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

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/s/

ANGELA H RAMSEY
09/19/2014



IND 74633

MEETING MINUTES

Vertex Pharmaceuticals
130 Waverly Street
Cambridge, MA 02139-4242

Attention: Antoinette Paone, MS, MBA
Senior Director, Regulatory Affairs CMC

Dear Ms Paone:

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

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2012. The purpose of the meeting was to discuss proposed pediatric formulation in the treatment of Cystic Fibrosis.

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 R.N., M.S.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: End-of Phase 2

Meeting Date and Time: December 12, 2012
Meeting Location: FDA White Oak Building 22, conference Room 1417

Application Number: 74633
Product Name: VX-770 (ivacaftor)
Indication: Treatment of Cystic Fibrosis
Sponsor/Applicant Name: Vertex pharmaceuticals

Meeting Chair: Prasad Peri, PhD., Quality Branch Chief
Meeting Recorder: Angela Ramsey R.N., M.S.N

FDA ATTENDEES
(tentative)

Prasad Peri, PhD., Quality Branch Chief
Alan Schroeder, PhD., CMC Lead
Arthur Shaw Ph.D., Quality Reviewer
Kimberly Witzmann, M.D., Clinical Reviewer
Anthony Witzmann, M.D., Clinical Team Leader
Meiyu Shen, Ph.D., Biometric Reviewer
Miya Paterniti, M.D., Clinical Reviewer
John Duan, Ph.D., Biopharmaceutical Reviewer

SPONSOR ATTENDEES

Meghan Johnston, Manager, Regulatory Affairs CMC
Antoinette Paone, M.S., MBA, Sr. Director, Regulatory Affairs CMC
Stephanie Krogmeier, Director, Regulatory Affairs CMC
Jennifer Dittmann, M.S., Associate Director, Regulatory Affairs
Hayden Thomas, Ph.D., Sr. Director, Formulation Development
Andrew Kuzmission, Ph.D., Director, Analytical Development
Ivelisse Colon-Rivera, Ph.D., Director, Technical Operations
Elizabeth Richmond, Associate Director, Technical Operations
Patrick Connelly, Ph.D., Principal Scientific Fellow
Robert Castellucci, Vice President, Quality Assurance

BACKGROUND

Vertex Pharmaceuticals submitted a Type C meeting request dated, October 9, 2012 to discuss proposed pediatric formulation in the treatment of Cystic Fibrosis. Vertex submitted background material dated, November 9, 2012. Upon review of the material, the Division responded via secure email on December 11, 2012. Vertex requested to continue with the face-to-face meeting to clarify responses to questions 1, 2, 3a, 3b, 5, and 6.

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. Vertex provided slide presentations to assist with discussion items (see attachment).

DISCUSSION

Question 1:

Considering Structured Product Labeling requirements and the definition of granule (NCI concept code C42938) and packet (NCI concept code (b) (4)) per the FDA Data Standards Manual, Vertex considers (b) (4) packaged in a foil laminated packet to fall under the administration route, dosage form and package type designation of oral granules in a packet. Does the Agency agree?

FDA Response:

Our recommendation will be provided when the labeling is submitted with the NDA.

Discussion:

The Division commented that there are very few granule formulations therefore labeling requirements will be a review issue.

Question 2:

Does the Agency agree with the approach to determine target fill count for the packet, specifically with adjusting the target fill count based on assay of the bulk (b) (4)?

FDA Response:

This will be a review issue depending upon the responses to the following Biometric questions:

- a. *Provide the procedure for calculating the following values: RSD_CU and RSD_analytical.*
- b. *Provide the derivation of Equation 2*
- c. *Submit the statistical model for derivation of Equation 2.*

- d. *Provide the values used for RSD_CU, RSD_analytical, a, and b in calculating probability shown in Table 4. Explain why these values are chosen for computation of probability in Table 4.*

Discussion:

Vertex provided clarification to their proposed approach referencing slides 15-22. The Division stated that the approach appears reasonable.

Question 3:

Does the Agency agree with the proposed release and stability testing strategy, specifically:

- a. *All release testing will be performed on the bulk (b) (4) except uniformity of dosage units (b) (4) which will be tested once (b) (4) have been filled into foil laminated packets.*

FDA Response:

This issue will be evaluated in your NDA when the following data are provided as you have indicated:

“As part of the Quality by Design (QbD) studies for this program, the effect of filling and packaging on assay and degradation products will be further evaluated to justify that assay and degradation testing on bulk (b) (4) is sufficient for release testing.”

Discussion:

The Division noted concerns with (b) (4) which could occur possibly during the packaging operation, and which could affect dissolution or disintegration. The Division stated that the surface to volume ratio is higher for granules (b) (4).

Vertex will assess and provide with the submission data from release testing of granules before and after filling into the packets to assess the effect of the packaging operation on the integrity of the granules. Vertex clarified that the data obtained for each batch of granules are used to determine the number of granules to fill into the packets to achieve the desired unit dose strength. The Division stated that the approach is acceptable assuming QbD studies are supported.

- b. *Analytical testing on stability will be performed on the contents of packaged units.*

FDA Response:

Yes.

Discussion:

See discussion in 3a.

Question 4:

Does the Agency agree with the proposed formal stability plan, specifically:

- a. Does the Agency agree that the bracketing stability design is supportive of all strengths between and inclusive of the low and high strengths studied?***

FDA Response:

The plan appears acceptable. However the data will be evaluated in the NDA submission to determine whether this approach can be used to support the expiration date labeling.

Discussion:

No discussion occurred.

- b. Does the Agency agree with the plan to supply the low and high bracketing strengths from the same three bulk lots of (b) (4) ?***

FDA Response:

The plan appears acceptable. However the data will be evaluated in the NDA submission to determine whether this approach can be used to support the expiration date labeling.

Discussion:

No discussion occurred.

- c. Does the Agency agree with the proposal to use the commercial batch size (b) (4) for formal stability studies?***

FDA Response:

The plan appears acceptable. However the data will be evaluated in the NDA submission to determine whether this approach can be used to support the expiration date labeling.

Discussion:

No discussion occurred.

- d. Does the Agency agree that a (b) (4) month drug product shelf life at the time of NDA may be justified provided the following data meets the proposed drug product specifications:***
- i. Eighteen months of formal stability on (b) (4) (3 batches) packaged in foil laminated packets.***
- ii. Two years of development (b) (4) stability packaged in foil laminated packets manufactured from (b) (4)***

FDA Response:

The plan appears acceptable. However, the data will be evaluated in the NDA submission to determine whether this approach can be used to support the expiration date labeling.

Discussion:

No discussion occurred.

Question #5

Does the Agency agree that the proposed dissolution method is biorelevant and suitable for primary stability studies and release of drug product?

FDA Response:

We agree that the dissolution method can discriminate for the formulation changes made to the Phase 3 formulation. However, there is insufficient information to classify your proposed dissolution method as biorelevant due to the following:

- There is no statistical analysis (e.g. 90% CI for relevant PK parameters, Cmax and AUC) provided in the meeting package.
- There is no data showing bioequivalence between the (b) (4) phase 3 formulation and Kalydeco under fasting conditions. (cross-study comparison resulted in point estimates close to failing at (b) (4)).
- In general, the FDA prefers that the “biorelevance designation” of the method relies on BE data generated taking into consideration the same formulation (e.g. prototype (b) (4) vs. phase 3 (b) (4)).
- There is no data on the ability of the method to discriminate for batches manufactured taking into consideration meaningful alterations in the critical quality attributes (b) (4).
- The designation of “biorelevance” is not only determined by the dissolution method alone, but in combination to the proposed acceptance criterion (see response to Q6).

Discussion:

Vertex requested the Division to clarify the term biorelevance. The Division stated that a biorelevant dissolution method should rely on bioequivalence (BE) data obtained from study under fasting conditions since the food effect is formulation dependent. When evaluating a dissolution method based on BE data, the food effect should be excluded. Vertex referenced page 6 of handout and proposed developing a clinically relevant dissolution method and acceptance criteria. The Division stated that the dissolution method appears reasonable, but the acceptance criteria may need further evaluation (see response to Q6).

Question 6

The proposed specification will take into account the dissolution performance (mean and variability) of the batches representative of the pivotal phase 3 clinical and primary stability batches and will reject the prototype (b)(4) with low bioavailability, as described above. Using currently available data as provided above, a specification of $Q = \frac{(b)(4)}{(4)}\%$ at $\frac{(b)(4)}{(4)}$ minutes would be consistent with these requirements. Does the Agency agree with this proposed approach to setting a biorelevant dissolution specification?

FDA Response

We agree with your proposal of setting dissolution acceptance criterion for the granules based on the dissolution performance (mean and variability) of the batches representative of the pivotal phase 3 clinical and primary stability batches. However, a dissolution acceptance criterion of $Q = \frac{(b)(4)}{(4)}\%$ at $\frac{(b)(4)}{(4)}$ min would not be considered biorelevant for the following reasons:

- The mean dissolution profile of the reference biobatch (Kalydeco 150 mg) is about $\frac{(b)(4)}{(4)}\%$ at $\frac{(b)(4)}{(4)}$ min not $\frac{(b)(4)}{(4)}\%$ at $\frac{(b)(4)}{(4)}$ min.*
- There is no information (e.g. phase 3, vs. commercial, etc) of the Kalydeco batches tested using the new dissolution method)*
- Assumption of in vivo BE (e.g. Kalydeco vs. phase 3 granules) is being made under fed conditions*
- Assumption of in vivo BE is being made using a different dosage form (e.g. tablet instead of granules)*
- The product contains a low solubility drug substance*

Discussion:

See discussion under question 5

Additional Comments

- Provide dissolution profiles as a function of (b)(4) content. These data is needed to further support the discriminating ability of the method and to set the appropriate dissolution acceptance criterion that is adequate to monitor for (b)(4) content.*
- Your intend to further support the dissolution acceptance criterion by use of a model relating dissolution to bioavailability should be reconsidered due to the following reasons:*
 - The linear model was constructed considering only two points (e.g. two release rates).*
 - The PK parameters used to construct the linear model are from a study conducted under fed conditions*

- *AUC_{inf} was used instead of AUC_t.*
- *The suitability of proposed soft foods as administration vehicles for your proposed drug product should be assessed by demonstrating that stability and release of the drug are preserved in the selected foods. Submit primary batch stability data in your NDA from these studies after mixing in the food matrix held for a period of time to cover the in-use period. It is recommended that you perform this stability testing on primary stability batches as a part of the formal stability studies at initial and final time points and at 12 months or the last time point for which data will be available. At a minimum, include testing for assay, impurities, and dissolution using appropriate validated analytical procedures*

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. 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. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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>

ATTACHMENTS AND HANDOUTS (include slides)

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

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
01/04/2013