

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203188Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 203188	
		NAME OF APPLICANT/NDA HOLDER VERTEX PHARMACEUTICALS INCORPORATED	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) KALYDECO			
ACTIVE INGREDIENT(S) ivacaftor		STRENGTH(S) 150 mg	
DOSAGE FORM Light blue, film-coated, capsule shaped tablets printed with the characters "V 150" in black ink on one side and plain on the other.			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,495,103		b. Issue Date of Patent FEBRUARY 24, 2009	c. Expiration Date of Patent MAY 20, 2027
d. Name of Patent Owner VERTEX PHARMACEUTICALS INCORPORATED		Address (of Patent Owner) 130 WAVERLY ST.	
		City/State CAMBRIDGE, MA	
		ZIP Code 02139	FAX Number (if available) Not Applicable
		Telephone Number 617-444-6100	E-Mail Address (if available) stephen_nesbitt@vrtx.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)		
2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)		
3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use		
<i>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</i>		
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2	Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
5. No Relevant Patents		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	OCTOBER 10, 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name STEPHEN L. NESBITT	
Address 130 WAVERLY ST.	City/State CAMBRIDGE, MA
ZIP Code 02139	Telephone Number 617-444-6100
FAX Number (if available) Not Applicable	E-Mail Address (if available) stephen_nesbitt@vrtx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 203188

SUPPL #

HFD #

Trade Name Kalydeco

Generic Name Ivacaftor

Applicant Name Vertex Pharmaceuticals

Approval Date, If Known 1-31-12

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#

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:

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 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:

- 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:

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: Miranda Raggio

Title: Senior Regulatory Project Managr

Date: 12-30-11 Cleared by Sandy Barnes, 1-20-12; Lee Ripper 1-26-12

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.

Title: Director, DPARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

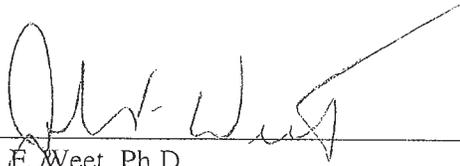
/s/

MIRANDA B RAGGIO
01/27/2012

BADRUL A CHOWDHURY
01/31/2012

DEBARMENT CERTIFICATION

Vertex Pharmaceuticals Incorporated hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Date 3 Oct, 2011

John F. Weet, Ph.D.
Vice President, Regulatory Affairs
Vertex Pharmaceuticals Incorporated

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

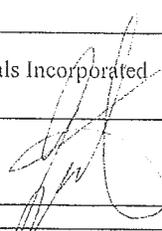
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Annex 1	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Ian Smith	TITLE Executive Vice President & CFO
FIRM/ORGANIZATION Vertex Pharmaceuticals Incorporated	
SIGNATURE 	DATE (mm/dd/yyyy) 10/7/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

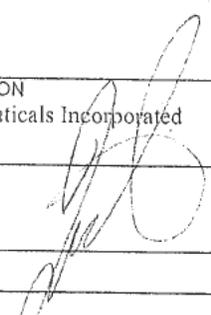
The following information concerning (b) (6), who participated
name of clinical investigator
as a clinical investigator in the submitted study VX08-770-102
Name of

clinical study _____ is submitted in accordance with 21 CFR part 54. The
named individual has participated in financial arrangements or holds financial interests that are
required to be disclosed as follows:

Please mark the applicable check boxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Ian Smith	TITLE Executive Vice President & CFO
FIRM/ORGANIZATION Vertex Pharmaceuticals Incorporated	
SIGNATURE 	Date (mm/dd/yyyy) 10/10/11

Paperwork Reduction Act Statement

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Department of Health and Human Services
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Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

1 **DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Physician:

(b) (6)

Address:

(b) (6)

(b) (6)

who participated in the ivacaftor VX08-770-102 study has compensation to report which meets the criteria defined in 21 CFR Part 54.

(b) (6)

Steps taken to minimize bias included conducting randomized controlled clinical trials and use of independent data monitoring board.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203188 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Kalydeco Established/Proper Name: Ivacaftor Dosage Form: 150mg tablets		Applicant: Vertex Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Miranda Raggio		Division: DPARP
<p>NDA: 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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>4-18-12</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

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><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</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² 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.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
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 (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval 1-31-12
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	10-18-11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input 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. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	10-18-11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	10-18-11(original),
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Review: 12-30-11 Letter: 12-30-11
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 12-30-11 <input checked="" type="checkbox"/> DMEPA 1-3-12 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 1-6-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 12-28-11(DMPP)
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing 12-30-11
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i>	10/20/11, 11/10/11, 12-14-11, 12-22-11(CMC IR), 12-22-11(labeling fax), 1-3-12, 1-6-12, 1-11-12(3), 1-12-12, 1/18/12, 1/19/12, 1/19/12, 1/20/12(CMC Advice letter),1/20/12(labeling fax), 1/25/12. 1-27-12
❖ Internal memoranda, telecons, etc.	1-13-12
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 6/12/11
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 9/18/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	Peds Pop 3/25/11, EOP1 6/30/08
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1-30-12
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1-27-12
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1-27-12, addendum 1-30-12
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 1-26-12
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	11-23-11, 11-29-11, 1-17-12
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<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>	1-17-12 Clinical Review Page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None 12-29-11(CDRH), 1-9-12(IRT)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<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
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 1-9-12
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
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"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/2/11, 1-13-12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/4/11, 1/18/12
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-27-12
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/17/12, 1-24-12(addendum), addendum 1-30-12
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/29/11, 1/3/12(carc), 1/6/12(repro), 1/13/12, 1-17-12
❖ 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 type="checkbox"/> No carc 12-23-11
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 12-21-11 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI 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"/> None 1-20-12
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/20/11(1), 10/20/11(2), 12-5-11(Biopharm) 12-16-1, 1/18/12(CMC), 1/18/12(biopharm)
❖ Microbiology Reviews <input 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 (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None 1-13-12
❖ 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>	1/18/12 Review, page 189
<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) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: 1/17/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (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 checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

MIRANDA B RAGGIO
01/31/2012

NDA 203188
Labeling Fax #5



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

FACSIMILE CORRESPONDENCE

Date: January 27, 2012

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

Secure Email: Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 Labeling Fax #5 (Kalydeco)

of Pages: 15

Comments: Please call with any questions. Thanks, miranda

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NDA 203188
Labeling Fax #5

Your labeling submission dated January 26, 2012, to NDA 203188, has been reviewed. Submit revised labeling incorporating changes in the attached marked-up label, making any required grammatical changes.

Submit a response via email to Miranda.Raggio@fda.hhs.gov by 9am on January 30, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188
Labeling Fax #5

Drafted by Miranda Raggio/1-25-12
Initialed by Sandy Barnes/ 1-25-12
Tony Durmowicz/1-25-12
Finalized by Miranda Raggio/1-25-12

13 Pages of Draft Labeling
have 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/

MIRANDA B RAGGIO
01/27/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Assess the impact of ivacaftor administration on exposure of co-administered P-gp substrates in an *in vivo* trial with a sensitive P-gp substrate, such as digoxin.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2012</u>
	Study/Trial Completion:	<u>06/30/2013</u>
	Final Report Submission:	<u>12/31/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Ivacaftor therapy provides substantial benefit to cystic fibrosis patients over current therapy; therefore it meets unmet medical need criteria. Only few patients with cystic fibrosis will be taking the P-gp substrate drugs along with ivacaftor; therefore, only a small subpopulation will be affected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In vitro studies indicate that ivacaftor has potential to inhibit P-gp, by which it can increase the exposure of co-administered P-gp substrates. The degree of change in exposure of P-gp substrates is unknown, but it could be substantially high requiring adjustments in the dose of co-administered P-gp substrates (such as digoxin, sirolimus, saxagliptin, and sitagliptin). These high exposures might present a safety risk. The goal of this study is to get a quantitative estimate of the change in exposure of P-gp substrates following co-administration with ivacaftor.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a single dose pharmacokinetic drug-drug interaction study in healthy subjects.
--

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
01/26/2012



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II**

FACSIMILE CORRESPONDENCE

Date: January 25, 2012

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

**Secure
Email:** Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 Labeling Fax #3 (Kalydeco)

of Pages: 13

Comments: Please call with any questions. Thanks, miranda

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NDA 203188
Labeling Fax #4-Final

Your labeling submission dated January 23, 2012, to NDA 203188, has been reviewed. Submit revised labeling incorporating changes in the comments below and in the attached marked-up/comments inserted labels. Additional labeling changes may be forthcoming.

Precribing Information

Section 6 Adverse Reactions

6.1 Clinical Trials Experience

Laboratory Abnormalities: We have edited the “*Transaminase Elevation*” section. For fair balance, we have added information related to transaminase elevation-related SAEs and have deleted the following:



Section 12 Clinical Pharmacology

12.2 Pharmacodynamics

We do not agree with deletion of the sentence which states that a change in sweat chloride does not correlate with change in FEV1. Analyses both by FDA and Vertex have confirmed that there is no correlation. Given the central role that sweat chloride levels have in the diagnosis of cystic fibrosis (CF) and as a potential biomarker of CFTR activity, we feel that information on the lack of correlation between changes in sweat chloride and lung function as measured by FEV1 is important information for physicians caring for patients with CF to have.

Patient Package Information (PPI)

The PPI submitted on January 23, 2012, is acceptable.

Carton and Container Labels

The carton and container labels submitted on January 16, 2012, are acceptable.

NDA 203188
Labeling Fax #4-Final

Submit a response via email to Miranda.Raggio@fda.hhs.gov by COB on January 26, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188
Labeling Fax #4-Final

Drafted by Miranda Raggio/1-25-12
Initialed by Sandy Barnes/ 1-25-12
Tony Durmowicz/1-25-12
Finalized by Miranda Raggio/1-25-12

9 Pages of Draft Labeling
have been Withheld in Full as
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/s/

MIRANDA B RAGGIO
01/25/2012

NDA 203188
Labeling Fax #3



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II**

FACSIMILE CORRESPONDENCE

Date: January 20, 2012

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

**Secure
Email:** Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 Labeling Fax #3 (Kalydeco)

of Pages: 19

Comments: Please call with any questions. Thanks, miranda

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Your submissions dated October 18, and December 27 and 29, 2011, and January 6, 9, 11, and 16 2012, to NDA 203188, are currently under review. We are providing preliminary labeling comments. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes in the comments below and in the attached marked-up/comments inserted labels. Note that some comments below are explanatory only.

Highlights and Package Insert (PI)

General Comment

1. Format changes have been made throughout the Highlights and PI in order to better comply with the PLR labeling format.

Prescribing Information

Section 7 Drug Interactions (7.1)

2. The dosing for patients who are taking concomitant strong CYP3A inhibitors was changed from (b) (4) to twice-a-week. This change was made in order to make it easier for patients to remember when to take a dose (e.g., every Sunday and Wednesday).

Section 8 Use in Specific Populations (8.6)

3. Dosing recommendation for patients with severe hepatic impairment was changed from (b) (4) to “use with caution at a dose of 150 mg once daily or less frequently in patients with severe hepatic impairment after weighing the risks and benefit of treatment” in order that, if appropriate caution is used, that patients with severe hepatic impairment may potentially benefit from Kalydeco. This recommendation has also been changed in other sections of the label.

Section 12 Clinical Pharmacology (12.3)

4. Figure 1: In the “Recommendation” column, first paragraph, please change the word “and” in the phrase “and P-gp substrates” to “and/or”.
5. Figure 2: For first recommendation regarding co-administration of strong CYP3A inhibitors, make the following change: “150 mg KALYDECO twice-a-week (remove (b) (4) when used with strong inhibitors....”. Also, in Figure 2 change the x-axis to read: “Change Relative to Reference (log-scale)”.

Section 14 Clinical Studies (14.1)

6. An explanation of how the CFQ-R respiratory domain was used was added to this section.

NDA 203188
Labeling Fax #3

Patient Package Information (PPI)

7. Examples of fat-containing food were added..
8. The month (tentative) and year of approval were added.

Carton/Container Labeling: Bottle Carton

9. Modify the bottle carton to show a provision for the lot number and expiry date.

Submit a response via email to Miranda.Raggio@fda.hhs.gov by COB on January 23, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188
Labeling Fax #3

Drafted by Miranda Raggio/1-20-12

Initialed by Sandy Barnes/ 1-20-12

Tony Durmowicz/1-20-12

(note: Carton and Container comment cleared previously via email from Alan Schroder and Prasad Peri)

Finalized by Miranda Raggio/1-20-12

15 Page(s) of Draft
Labeling have been
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/s/

MIRANDA B RAGGIO
01/20/2012



NDA 203188

GENERAL ADVICE

Vertex Pharmaceuticals, Inc.
Attention: Marjorie A. Egan, Ph.D.
Director, Global Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Dr. Egan:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-770 (ivacaftor) Tablets.

We have reviewed the Chemistry, Manufacturing, and Controls information and have the following comments. No additional response to the application is required.

- The provided information/data (e.g. dissolution profiles comparison with f_2 statistical testing) is still insufficient to determine whether batches manufactured throughout the drug product design space (DS) would result in products that are bioequivalent. The f_2 comparisons provided on January 13, 2012 did not consider all possible combinations within the proposed DS [REDACTED] ^{(b) (4)}. Therefore, consider performing dissolution profile comparisons with f_2 testing for movements outside of the NOR and within your proposed design space for commercial batches manufactured after approval. This may be handled within your internal quality control system.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ERIC P DUFFY
01/20/2012



NDA 203188

**METHODS VALIDATION
MATERIALS RECEIVED**

Vertex Pharmaceuticals Inc.
Attention: Marjorie Egan, PH.D.
Director, CMC Regulatory Affairs
130 Waverly Street
Cambridge, MA 02139-4242

Dear Dr. Marjorie Egan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kalydeco (Ivacaftor) Tablets, 150 mg and to our 1/11/2012 and 1/17/2012, electronic letters requesting sample materials for methods validation testing.

We acknowledge receipt on 1/13/2012 and 1/19/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
01/19/2012



NDA 203188

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Vertex Pharmaceuticals Incorporated
Attention: Marjorie Egan, Ph.D.
Director, CMC Regulatory Affairs
130 Waverly Street
Cambridge, MA 02139

Dear Dr. Egan

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kalydeco (ivacaftor) tablets 150 mg.

We will be performing methods validation studies on Kalydeco (ivacaftor) tablets 150 mg, as described in NDA 203188.

We have been requested to validate an additional method. In order to perform the necessary testing, we request the following sample materials and equipments:

Samples and Reference Standards

150 mg	Ivacaftor (VX-770) Drug Substance
--------	-----------------------------------

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
01/19/2012



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

FACSIMILE CORRESPONDENCE

Date: January 18, 2012

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

**Secure
Email:** Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 (Kalydeco) PMR Fax #1

of Pages: 3

Comments: Please call with any questions. Thanks, Miranda

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Your submission dated October 18, 2011, to NDA 203188, is currently under review. We have the following request related to a post-marketing requirement (PMR):

In vitro studies indicate that ivacaftor has the potential to inhibit P-gp, by which it can increase the exposure of co-administered P-gp substrates. The degree of change in exposure of P-gp substrates is unknown, but it could be substantially high, requiring adjustments in the dose of co-administered P-gp substrates. In the absence of dose adjustments, these high exposures might present a safety risk. Therefore, we are requiring the following post-marketing requirement:

Assess the impact of ivacaftor administration on exposure of co-administered P-gp substrates in an in vivo study with a sensitive P-gp substrate, such as digoxin.

Submit a statement indicating your intent to comply with the above proposed PMR and provide the following timelines:

- Final Protocol Submission
- Trial Completion
- Final Report Submission

Submit a response via email to Miranda.Raggio@fda.hhs.gov by noon on January 19, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188 PMR Fax #1

Drafted by Miranda Raggio/1-18-12

Initialed by Sandy Barnes/ 1-18-12

Tony Durmowicz/1-18-12

Suresh Doddapaneni/1-18-12

Sally Seymour/1-18-12

Finalized by Miranda Raggio/1-18-12

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/s/

MIRANDA B RAGGIO
01/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: NAME, Arthur B. Shaw, Ph.D., CMC Reviewer
NAME, Alan Schroeder, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: arthur.shaw@fda.hhs.gov
Phone: (301)-796-1460
Fax.: (301)-796-9747

Through: NAME, Alan Schroeder, Ph.d.
Phone: (301)-796-1749

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203188

Name of Product: Kalydeco (ivacaftor) tablets 150 mg

Applicant: Vertex Pharmaceuticals Incorporated.

Applicant's Contact Person: John F. Weet, PhD, Vice President, Regulatory Affairs

Address: 130 Waverly Street, Cambridge, MA 02139

Telephone: 617-444-7789 Fax: 617-444-6803

Date NDA Received by CDER: **7/27/2011**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **07/27/2011**

Special Handling Required: No

DATE of Request: **January 12, 2012**

DEA Class: N/A

Requested Completion Date: **1/25/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **4/18/2012**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 203188
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Ivacaftor drug substance	to be requested	To be requested		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				N/A
Specifications/Methods for New Drug Substance(s)				3.2.S.4
Specifications/Methods for Finished Dosage Form(s)				N/A
Supporting Data for Accuracy, Specificity, etc.				3.2.P.S.4
Applicant's Test Results on NDS and Dosage Forms				3.2.P.S.5
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
GC-MS	Test for (b) (4)	3.2.S.4	4	Sensitive GC-MS method
t				
Additional Comments: Control of (b) (4) is important to the quality of the drug substance.				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

ARTHUR B SHAW

01/13/2012

This is an additional request for testing a (b) (4) impurity in the drug substance

ALAN C SCHROEDER

01/13/2012

JEANNIE C DAVID

01/13/2012

ONDQA Methods Validation Project Manager



NDA 203188

INFORMATION REQUEST

Vertex Pharmaceuticals, Inc.
Attention: Marjorie A. Egan, Ph.D.
Director, Global Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Dr. Egan:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-770 (ivacaftor) Tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 20 min is not acceptable as it does not provide satisfactory assurance of bioequivalence to the clinical batches, based on f_2 testing. This specification value would accept batch A4020-146 (shown as H27.6 BD0.27 in Figure 1) (b) (4)

Therefore
The following dissolution acceptance criterion is recommended for Ivacaftor IR, Tablets 150 mg.

- $Q = \frac{(b)}{(4)}\%$ in 15 min

This dissolution acceptance criterion was established based on the following information: (b) (4)



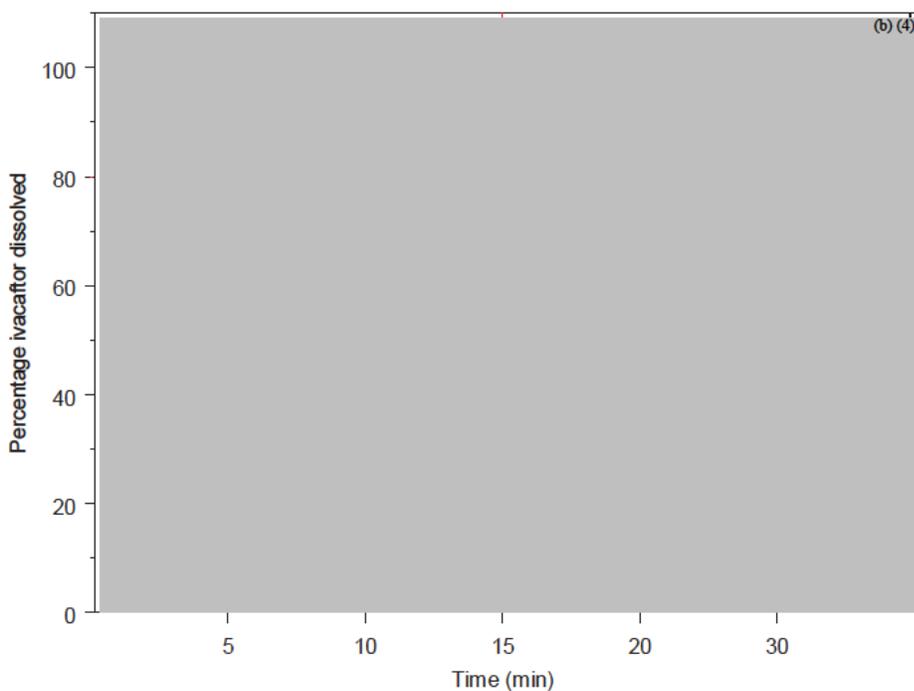


Figure 1. Effect of Hardness on Dissolution of Ivacaftor Tablets, 150 mg . (b) (4)
(b) (4)
(b) (4). Generated from data submitted on Dec 22, 2011 and Jan 9, 2012.

- b. Mean dissolution values from the clinical drug product release and the drug product stability testing.
 - The mean percentage dissolved of all the batches (b) (4) at 15 minutes (Figure 2).

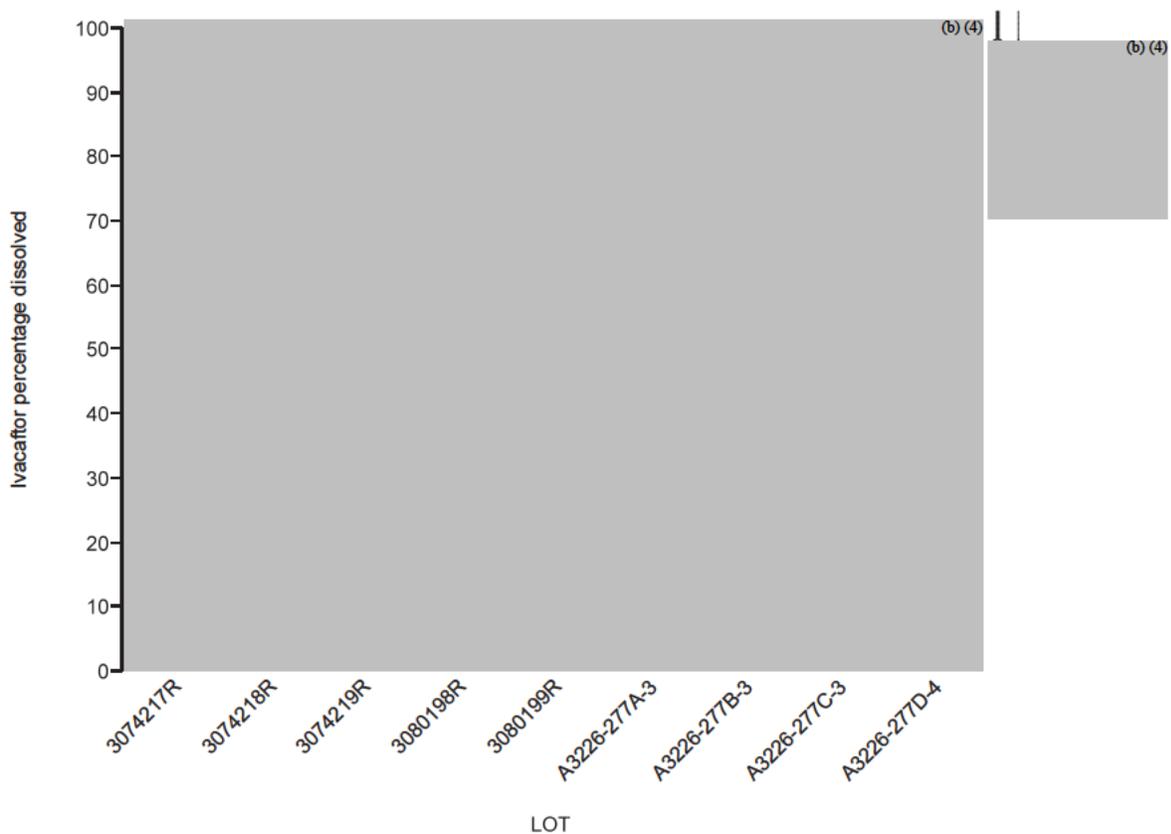


Figure 2. Ivacaftor mean dissolution profiles from the clinical and primary stability batches (up to 9 months) supporting the selection of the dissolution acceptance criterion. Generated using data submitted on Dec 22, 2011.

Hence, revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications reflecting this change.

2. To facilitate the implementation of our recommended dissolution specification, the Agency recommends the following dissolution specification and time point (b) (4) (b) (4) (b) (4) analysis in the control of (b) (4)

- Mean of (b) (4) in 15 minutes

Alternatively, your proposed specification of mean of (b) (4) in 20 minutes (b) (4) (b) (4) (b) (4) is acceptable.

3. Your proposed design space for tablet hardness is not acceptable because it was determined based on a model that considered a (b) (4) (b) (4)
 - a. Under these assumptions, the model predicts acceptable dissolution performance for a batch (A4020-146) that fails f_2 testing (b) (4)

- b. Therefore, determine if the PAR specifications for tablet hardness need revision considering a revised dissolution acceptance criterion (e.g. $Q = \frac{(b)}{(4)}\%$ at 15 min).

There were insufficient data (e.g. dissolution profiles comparison with f_2 statistical testing, *in vitro in vivo* correlation (IVIVC) models, or *in vivo* bioequivalence studies) to determine whether batches manufactured throughout the drug product design space would result in products that are bioequivalent. Therefore, we recommend performing dissolution profile comparisons with f_2 testing for any movements outside the NOR and within your proposed design space.

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/s/

DON L HENRY
01/12/2012



NDA 203188

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Vertex Pharmaceuticals Incorporated
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
130 Waverly Street
Cambridge, MA 02139

Dear Dr. Weet

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kalydeco (ivacaftor) tablets 150 mg.

We will be performing methods validation studies on Kalydeco (ivacaftor) tablets 150 mg, as described in NDA 203188.

In order to perform the necessary testing, we request the following sample materials and equipments:

Samples and Reference Standards

(b) (4) Kalydeco (ivacaftor) tablets 150 mg

(b) (4)

(b) (4)

(b) (4)

Equipment (These will be returned)

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
01/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: NAME, Arthur B. Shaw, Ph.D., CMC Reviewer
NAME, Alan Schroeder, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: arthur.shaw@fda.hhs.gov
Phone: (301)-796-1460
Fax.: (301)-796-9747

Through: NAME, Alan Schroeder, Ph.d.
Phone: (301)-796-1749

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203188

Name of Product: Kalydeco (ivacaftor) tablets 150 mg

Applicant: Vertex Pharmaceuticals Incorporated.

Applicant's Contact Person: John F. Weet, PhD, Vice President, Regulatory Affairs

Address: 130 Waverly Street, Cambridge, MA 02139

Telephone: 617-444-7789 Fax: 617-444-6803

Date NDA Received by CDER: **7/27/2011**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **07/27/2011**

Special Handling Required: No

DATE of Request: **January 10, 2012**

DEA Class: N/A

Requested Completion Date: **1/25/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **4/18/2012**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 203188
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Kalydeco tablets	to be requested	To be requested		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1 and 5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.P.5.6
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
Dissolution of tablet	Dissolution of Tablets	3.2.P.5.2	4	Standard dissolution method
Physical Form of tablet	(b) (4)	3.2.P.5.2	4	
Assay and impurities in tablet	HPLC	3.2.P.5.2	0	HPLC method is different from the HPLC method used in the Dissolution test
Additional Comments: This drug is present in an (b) (4), in the finished dosage form. (b) (4)				
The clinical division is aiming for an early action by the end of January 2012. Validation of the methods is not critical to approval of the drug.				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

ARTHUR B SHAW
01/10/2012

ALAN C SCHROEDER
01/10/2012
I concur

PRASAD PERI
01/10/2012

JEANNIE C DAVID
01/11/2012
ONDQA Methods Validation Project Manager

NDA 203188
Labeling Fax #2



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

FACSIMILE CORRESPONDENCE

Date: January 11, 2012

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

**Secure
Email:** Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 Labeling Fax #2 (Kalydeco)

of Pages: 24

Comments: Please call with any questions. Thanks, miranda

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Your submissions dated October 18, and December 27 and 29, 2011, and January 6, 2012, to NDA 203188, are currently under review. We are providing preliminary labeling comments. Additional labeling changes will be forthcoming. Submit revised labeling incorporating changes in the comments below and in the attached marked-up/comments inserted labels:

Package Insert (PI)

1. Section 6, Adverse Reactions (6.1) Table 1: Adverse reaction information was revised to "Incidence of Adverse Reactions in \geq 8% of KALYDECO-Treated Patients." Revise the list of less frequent adverse reactions to reflect those that occurred in the KALYDECO group at a frequency of 4 to 7% where rates exceeded that in the placebo group.
2. Sections 12, Clinical Pharmacology (12.3) and 17, Patient Counseling Information (17.4): Give specific examples of the types of fat-containing food appropriate to administer KALYDECO with.

Carton/Container Labeling

General Comments on all container labels and carton labeling

3. Ensure the presentation of the established name is at least $\frac{1}{2}$ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).
4. Increase the prominence and relocate the strength statement to immediately follow the proprietary and established names. For example:

Kalydeco
(Ivacaftor) Tablets
150 mg

Container label (60-count bottle)

5. Decrease the prominence and relocate the net quantity statement (i.e. '60 tablets') so that it appears separate from the product strength.
6. Remove the phrase [REDACTED] ^{(b) (4)} to reduce clutter and improve readability of other important information on the label.
7. Revise the statement [REDACTED] ^{(b) (4)} to read "Usual Dosage: See Prescribing Information."

Blister Card Label

8. Increase the size and prominence of the strength statement '150 mg'.

Carton Labeling (60-count bottle and blister cards)

9. Relocate the net quantity statement '60 tablets' and '56 tablets' so that it appears on the principal display panel but away from the product strength.

10. Revise the statement [REDACTED] (b) (4) to read "Usual Dosage: See Prescribing Information."

11. Remove or reduce the prominence of the graphic located on the lower portion of the carton labeling as it distracts from the most important information such as the proprietary name, established name, and strength statements.

Carton Labeling for Blister Card Only

12. Revise the statement [REDACTED] (b) (4) to read "Carton contains 4 individual blister cards of 14 tablets per card."

13. Revise the strength statement to read "150 mg per tablet". For example:

Kalydeco
(Ivacaftor) Tablets
150 mg per tablet

Patient Assistance Program Sticker Placement

14. The placement of the proposed sticker to be attached to each Kalydeco unit carton shipped to patients under Vertex's Patient Assistance Program is acceptable.

Patient Package Information (PPI)

15. In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In addition, in editing the PPI, we have:

- simplified wording and clarified concepts, where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

NDA 203188
Labeling Fax #2

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

(b) (4)

Submit a response via email to Miranda.Raggio@fda.hhs.gov by 9am on January 17, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188
Labeling Fax #2

Drafted by Miranda Raggio/1-11-12
Initialed by Sandy Barnes/ 1-11-11
Tony Durmowicz/1-11-12

Finalized by Miranda Raggio/1-11-12

19 Pages of Draft Labeling have
been Withheld in Full as b4 (CCI/
TS) immediately following this
page

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/s/

MIRANDA B RAGGIO
01/11/2012

Henry, Don

From: Henry, Don
Sent: Tuesday, January 10, 2012 11:43 AM
To: 'Marjorie_Egan@vrtx.com'
Cc: Antoinette_Paone@vrtx.com; Raggio, Miranda
Subject: NDA 203188 Information request

Marjorie

Please find a follow-up request regarding you tablet hardness:

- Confirm if all the clinical batches were produced within the NOR for hardness and bulk density. If not, provide the values of hardness and bulk density for all the clinical batches.

Thank you

Don L. Henry
Food and Drug Administration
CDER/Office of New Drug Quality Assessment
Phone: 301-796-4227
Don.Henry@fda.hhs.gov

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/s/

DON L HENRY
01/11/2012



NDA 203188

INFORMATION REQUEST

Vertex Pharmaceuticals, Inc.
Attention: Marjorie A. Egan, Ph.D.
Director, Global Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Dr. Egan:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-770 (ivacaftor) Tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide data regarding the (b) (4) ivacaftor. Submit the data to section 3.2.S.3.1 of the application
2. Provide the basis for the following statement in the December 29, 2011 amendment, "It is hypothesized that these high levels of (b) (4) (b) (4) of ivacaftor to (b) (4) Submit the information to section 3.2.P.5.5 of the application.
3. Include measured levels of (b) (4) in the batches of drug product manufactured up until now and the levels observed on stability. Submit the information to section 3.2.P.5.5 of the application
4. Provide justification for the PAR and NOR for hardness based on the currently proposed dissolution acceptance criteria.
5. In your December 29, 2011, amendment, you stated,
"The reagents and solvents used in the drug substance synthesis are all readily available from commercial sources. The current specifications in place at the drug substance manufacturer meet the requirements in Table 2 below, which are provided for information only. These tests may be performed at the drug substance manufacturer or accepted on supplier's certificate of analysis. The regulatory commitments for the critical tests are included in NDA Section 3.2.S.2.3 Control of Materials - Reagents and Solvents, Table 2 (Seq 0000) and remain unchanged."
Explain what is meant by "For information only". Explain why the specifications in section 3.2.S.2.3 were not included.
6. Provide the locations in the NDA of any experiments to support accepting the solvents and reagents simply on the basis of commercial availability.

7. Provide the specifications for accepting  (b) (4)


If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

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/s/

DON L HENRY
01/06/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Thursday, January 5, 2012
TIME: 15:30 – 16:30 ET
LOCATION: Teleconference
APPLICATION: NDA 203188
DRUG NAME: ivacaftor tablets

FDA ATTENDEES: (Title and Office/Division)

Eric Duffy, Division Director, ONDQA
Prasad Peri, Branch Chief, ONDQA
Arthur Shaw, Product Quality Reviewer, ONDQA
Alan Schroeder, CMC Lead, ONDQA
Sandra Suarez, Biopharmaceutics Reviewer, ONDQA
Miranda Raggio, Senior Regulatory Health Project Manager, DPARP
Don Henry, Regulatory Project Manager, ONDQA

VERTEX ATTENDEES:

Juergen Froehlich, VP, Regulatory
Patricia Hurter, Sr. VP, Pharmaceutical Development
Dan Belmont, VP, Chemical Development
Mark DeRosch, Sr. Director, Regulatory
Tom Gandek, Sr. Director, Pharmaceutical Operations
Lisa Mahnke, Sr. Director, Clinical Pharmacology
Antoinette Paone, Sr. Director, Regulatory CMC
Kelly Tolton, Director, Pharmaceutical Operations
Geny Doss, Director, GMP Quality
Marjorie Egan, Director, Regulatory CMC
David Nadig, Sr. Director, Analytical Development
Drew Kuzmission, Director, Analytical Development
Majed Fawaz, Director, Materials Discovery and Characterization
Adam Looker, Associate Director, Chemical Development
Bill Rowe, Associate Director, Formulation Development

BACKGROUND:

The Agency scheduled a meeting with Vertex to discuss pending CMC concerns. The following discussion topics were sent to Vertex prior to the meeting:

1. Data regarding the (b) (4) ivacaftor.
2. Basis for the following statement in the Dec 29, 2011, amendment, "It is hypothesized that these high levels of (b) (4) of ivacaftor to (b) (4) ."
3. Include measured levels of (b) (4) in the batches of drug product manufactured up until now and the levels observed on stability.
4. Rationale for requesting additional dissolution data.
5. Recalculation of PAR and NOR for hardness if dissolution specification is changed. Changes to MBR to reflect the revised PAR/NOR.
6. In our Dec 14, 2011, IR letter, we requested, "Provide the specifications (tests, analytical procedures, and acceptance criteria) for the reagents and solvents used in the synthesis of ivacaftor."

The following response was provided:

"The reagents and solvents used in the drug substance synthesis are all readily available from commercial sources. The current specifications in place at the drug substance manufacturer meet the requirements in Table 2 below, which are provided for information only. These tests may be performed at the drug substance manufacturer or accepted on supplier's certificate of analysis. The regulatory commitments for the critical tests are included in NDA Section 3.2.S.2.3 Control of Materials - Reagents and Solvents, Table 2 (Seq 0000) and remain unchanged."

What is meant by "For information only"? The specifications in Section 3.2.S.2.3 are not included.

DISCUSSION POINTS AND ACTION ITEMS:

Vertex provided slides (attached) prior to the teleconference meeting to facilitate the discussion.

Topic #1: (see Vertex slides 2-5): The Agency concurred that the data presented adequately justifies (b) (4) ivacaftor. Vertex was requested to submit the information to the application in section 3.2.S.3.1, and the sponsor agreed to do so.

Topic #2: (see Vertex slide 6): The Agency agrees that since (b) (4), it (b) (4) of ivacaftor to (b) (4) Vertex was requested to submit the information to the application in section 3.2.P.5.5, and the sponsor agreed to do so.

Topic #3: (see Vertex slides 7-8): The Agency indicated that the information will be included as part of the risk assessment in determining the appropriate levels for the impurities. Vertex was requested to submit the information to the application in section 3.2.P.5.5, and the sponsor agreed to do so.

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/s/

DON L HENRY
01/13/2012

Henry, Don

From: Henry, Don
Sent: Tuesday, January 03, 2012 11:52 AM
To: 'Marjorie_Egan@vrtx.com'
Cc: Antoinette_Paone@vrtx.com; Raggio, Miranda
Subject: NDA 203188 dissolution data

Hello Marjorie

The following dissolution profile data cannot be located. Can you provide the location of this information or amend the application with the information

- dissolution profile data (raw data and mean values) for the drug product batches used in PK study VX08-770-007 (b) (4)

Thank you
Don

Don L. Henry
Food and Drug Administration
CDER/Office of New Drug Quality Assessment
Phone: 301-796-4227
Don.Henry@fda.hhs.gov

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/s/

DON L HENRY
01/03/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203188 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Kalydeco Established/Proper Name: Ivacaftor (VX-770) Dosage Form: Oral Tablets Strengths: 150mg		
Applicant: Vertex Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: 10-18-11 Date of Receipt: 10-18-11 Date clock started after UN:		
PDUFA Goal Date: 4-18-12		Action Goal Date (if different):
Filing Date: 12-17-11		Date of Filing Meeting: 11-9-11
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1-NME		
Proposed indication(s)/Proposed change(s): Cystic Fibrosis in patients > 6 yrs of age with a G551D mutation in the CFTR gene		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 74633				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	XX			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		XX		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th data-bbox="203 1446 495 1482">Application No.</th> <th data-bbox="495 1446 771 1482">Drug Name</th> <th data-bbox="771 1446 1060 1482">Exclusivity Code</th> <th data-bbox="1060 1446 1349 1482">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>	<p>YES</p>	<p>NO XX</p>	<p>NA</p>	<p>Comment</p>																

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	XX			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	XX			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	XX			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	XX			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	XX			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	XX			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	XX			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?				
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	XX			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			XX	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		XX		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	XX			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		XX		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	XX			
Is the PI submitted in PLR format? ⁴	XX			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	XX			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	XX			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	XX			
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 10-8-09 <i>If yes, distribute minutes before filing meeting</i>	XX			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 6-20-11 <i>If yes, distribute minutes before filing meeting</i>	XX			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		XX		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-9-11

BLA/NDA/Supp #: 203188

PROPRIETARY NAME: Kalydeco

ESTABLISHED/PROPER NAME: Ivacaftor(VX-770)

DOSAGE FORM/STRENGTH: 150mg Tablets

APPLICANT: Vertex Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Cystic Fibrosis in patients > 6 years of age with the G551D mutation in the CFTR gene

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Miranda Raggio	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Tony Durmowicz		Y
Clinical	Reviewer:	Kimberly Witzmann	Y
	TL:	Tony Durmowicz	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Partha Roy Atul Bhattaram (genomics)	Y
	TL:	Suresh Doddapaneni Yaning Wang(genomics)	N
Biostatistics	Reviewer:	David Hoberman	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcie Wood	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:	Steven Thomson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Art Shaw and Ying Wang	Y(Art Shaw Only)
	TL:	Alan Schroeder Prasad Peri	Y(both)
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	N
	TL:	Carlos Mena-Grillasca	N
OSE/DRISK (REMS)	Reviewer:	Robin Duer Dipti Kalra (DPV)	N
	TL:	Melissa Hulett Ann Corken(DPV)	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orenca	Y
	TL:	Susan Leibenhaut	N

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers			
Other attendees	Lydia Gilbert-McClain, DPARP Karen Bijawaard, CDRH Thomas Permutt, Biostatistics Robert Temple, DD, Clinical Science, OND Curt Rosebraugh, ODEII Maria Chen (phone), CDRH Andrea Tan, (phone)Risk-Benefit Pilot Reena Philip (phone), CDRH Liz Mansfield, CDRH Lisa Lavance, Biostatistics Anne Pariser, OND IO Lee Ripper, ODEII		Yes to all

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments:</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: 2-24-12 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>BIostatistics</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curt Rosebraugh, ODEII	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Miranda Raggio	11-10-11
Regulatory Project Manager	Date
Sandy Barnes	12-30-11
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MIRANDA B RAGGIO
12/30/2011



NDA 203188

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139

ATTENTION: John F. Weet, PhD
Vice President, Regulatory Affairs

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) dated October 18, 2011, received October 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ivacaftor Tablets, 150 mg.

We also refer to your October 18, 2011, correspondence, received October 18, 2011, 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 October 18, 2011, 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 the Office of New Drugs (OND) Regulatory Project Manager, Miranda Raggio at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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

/s/

IRENE Z CHAN on behalf of CAROL A HOLQUIST
12/30/2011

Consult Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration



Date: December 29, 2011

To: Kim Witzmann, M.D., Medical Officer and Tony Durmowicz, M.D., Clinical Team Leader, CDER/OND/ODEII/DPARP, and Miranda Raggio, BA, BSN, MA, Senior Regulatory Health Project Manager, CDER/OND/ODEII/DPARP

From: Karen Bijwaard, MS, RAC, MB(ASCP)^{CM}, Scientific Reviewer, CDRH/OIVD/DIHD Through Maria M. Chan, PhD, Director, CDRH/OIVD/DIHD

Re: CDRH consult request for NDA203188 Vertex Pharm., Inc., KALYDECO (Ivacaftor)

Intended Use from draft labeling provided on 12/16/11:

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients, age 6 years and older who have a G551D mutation in the CFTR gene. *If the patient's genotype is unknown, an FDA-cleared diagnostic test should be used to detect the presence of the G551D mutation.* (1)

Limitations of Use: KALYDECO has demonstrated efficacy only in patients with CF who have a G551D mutation in the CFTR gene. It is not effective in CF patients homozygous for the F508 mutation in the CFTR. (1, 14)

Consult request:

Vertex has submitted NDA# 203,188 for ivacaftor for treatment of cystic fibrosis in those with a G551D CFTR mutation. In your Pre-IDE Memorandum communication to the Sponsor on 7/29/2011, in your response to Question 1 from Vertex you noted it was acceptable to use 510(k)-cleared CF genotyping kits for identification of the G551D mutation. While DPARP agrees with your view on the use of FDA-approved genetic tests to identify the G551D mutation, Vertex has not included any reference to any type of genetic test in the proposed product label.

We therefore have the following questions:

1. Should any specific reference to the types of genetic testing for the G551D mutation be included in the product label?

[OIVD]: OIVD recommends that the use of an FDA-cleared cystic fibrosis mutation assay to identify the presence of the G551D mutation be referenced in the label. OIVD recommends following edit (in blue) to the intended use statement in the highlights and Section 1 of the KALYDECO (Ivacaftor) label:

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene. *If the patient's*

genotype is unknown, an FDA-cleared [cystic fibrosis mutation test](#) should be used to detect the presence of the G551D mutation.

2. If you feel that specific reference to the types of genetic test to be used should be included in the product label, would gene sequencing by a certified laboratory be acceptable in lieu of an FDA-approved test?

[OIVD]: No. There are laboratories that perform CF testing using laboratory developed tests (LDTs), some of which include gene sequencing methods, however CLIA does not stipulate or regulate the extent to which these test are validated prior to being placed in service. Therefore the extent of their validation and their performance are not known.

If you have any questions or comments regarding this review, please call me at (301) 796-6162 or email me at karen.bijwaard@fda.hhs.gov.

Karen E. Bijwaard

Digitally signed by Karen E. Bijwaard
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Karen E. Bijwaard,
0.9.2342.19200300.100.1.1=1300370837
Date: 2011.12.29 06:55:45 -05'00'

Karen Bijwaard, MS
Consulting Reviewer, CDRH/OIVD/DIHD/IMDB

cc: Maria M. Chan, PhD, Director, CDRH/OIVD/DIHD
Reena Philip, PhD, Deputy Director, CDRH/OIVD/DIHD
Yun-Fu Hu, PhD, Assoc. Director CDRH/OIVD/DIHD/IMDB
Elizabeth Mansfield, PhD, Director of Personalized Medicine, OIVD
Robert L. Becker, MD, PhD, Chief Medical Officer, OIVD

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/s/

MIRANDA B RAGGIO
12/29/2011
CDRH Completed Consult



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II**

FACSIMILE CORRESPONDENCE

Date: December 22, 2011

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

**Secure
Email:** Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 (ivacaftor), CMC Fax r/t [REDACTED] (b) (4)

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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Your submission dated October 18, 2011, to NDA 203188, is currently under review. We have the following information requests:

1. *Provide the data to support your statement that [REDACTED] ^{(b) (4)} is unstable.*
2. *Provide data from the forced degradation studies, with particular attention to the detection of [REDACTED] ^{(b) (4)}*
2. *Provide data to demonstrate the stability of [REDACTED] ^{(b) (4)} in the HPLC assay.*
3. *Provide data to support the assignment of the structure of the impurities.*

Submit a response via email to Miranda.Raggio@fda.hhs.gov by 9am on January 3, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188 CMC Fax 12-22-11

Drafted by Miranda Raggio/12-22-11

Initialed by Sandy Barnes/ 12-22-11

Art Shaw/12-22-11

Alan Schroeder/12-22-11

Finalized by Miranda Raggio/12-22-11

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/s/

MIRANDA B RAGGIO
12/22/2011



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II**

FACSIMILE CORRESPONDENCE

Date: December 22, 2011

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

**Secure
Email:** Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 Labeling Fax #1

of Pages: 20

Comments: Please call with any questions. Thanks, miranda

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Your submission dated October 18, 2011, to NDA 203188, is currently under review. We are providing preliminary labeling comments. Additional labeling changes, including clinical pharmacology and nonclinical label comments will be forthcoming. Submit revised labeling incorporating changes in the comments below and in the attached marked up label:

Package Insert (PI)

Highlights:

Revise the Adverse Reactions section based on the new adverse reactions information in Table 1. Confirm that the premature discontinuation data are correct.

Adverse Reactions:

6.1 Clinical Trials Experience

- Add demographic data regarding sex and race where indicated by “XX”.
- Revise the premature discontinuation information to reflect the full safety population (encompassing studies 102, 102, and 104).
- Confirm that the serious adverse reaction data reflects the full safety population.
- Add the most common adverse reaction information in text for CF patients that are observed in greater than or equal to 5% of Kalydeco-treated patients and greater than placebo for the full safety population.
- Revise the data in Table 1 to reflect the “Incidence of Adverse Drug Reactions in \geq 5% of KALYDECO-Treated Patients with a G551D Mutation in the CFTR Gene and $>$ than Placebo in 2 Placebo-Controlled Clinical Trials of 48 Weeks”.
- The composite term “upper respiratory tract infection events” used in Table 1 should be “ungrouped” to include the appropriate preferred term, e.g., nasal congestion, rhinitis, nasopharyngitis, etc.
- Include a section immediately following Table 1 that lists by system-organ-class adverse reactions that occurred in the Kalydeco group at a frequency of 1-4% where rates exceeded that in placebo group (see example in the attached proposed label).

Section 6.2 Description of Selected Adverse Reactions

- This section is reserved for post-marketing adverse reaction information. Since Kalydeco has not been yet marketed, Section 6.2 should be deleted. Information on respiratory tract infections and rash in the current Section 6.2 are already presented in Section 6.1. Transaminase elevations should be included in Section 6.1.

Section 14.1, Clinical Studies

- Revise study titles for Study 102 and Study 103 to Studies 1 and 2, respectively.

NDA 203188

Carton/Container Labeling

Remove the list of ingredients which make up Kalydeco as it distracts from other information on the carton label and necessitates too small a font.

Note that the attached labeling includes changes requested in the letter sent to you from DPARP on December 14, 2011.

Submit a response via email to Miranda.Raggio@fda.hhs.gov by 9am on January 3, 2012. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188

Drafted by Miranda Raggio/12-22-11
Initialed by Sandy Barnes/ 12-22-11
Tony Durmowicz/12-22-11

Finalized by Miranda Raggio/12-22-11

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

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/s/

MIRANDA B RAGGIO
12/22/2011

Executive CAC

Date of Meeting: December 20, 2011

Committee: David Jacobson Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Timothy Robison, Ph.D., Team Leader
Marcie Wood, Ph.D., Presenting Reviewer

Author of Minutes: Marcie Wood, Ph.D.

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

NDA # 203-188

Drug Name: Ivacaftor (VX-770)

Sponsor: Vertex Pharmaceuticals, Inc.

Background: Two-year mouse and rat carcinogenicity studies with VX-770 were conducted by [REDACTED] ^{(b) (4)}. The sponsor received ECAC concurrence for doses used with mice and rats (see Meeting Minutes dated January 27, 2009).

VX-770 was negative in a bacterial reverse mutation assay, a Chinese hamster ovary chromosomal aberration assay and in an in vivo mouse micronucleus assay.

Mouse Carcinogenicity Study: In a 2-year carcinogenicity study, VAF/Plus Crl:CD-1 (CR) BR mice received oral doses of VX-770 at 25, 75, and 200 mg/kg/day. Vehicle control groups (0.5% w/v methylcellulose with 0.5% w/v sodium lauryl sulfate in water) with and without 0.01% simethicone were also included in the study. No statistically significant test article-related tumor findings were observed. There were no test article-related effects on survival or body weight versus controls. Accumulation of VX-770 and metabolites M1 and M6 was observed in males and females by Months 6 and 12. In addition, systemic exposures of VX-770, M1, and M6 were generally greater in females than males.

Rat Carcinogenicity Study: In a 2-year carcinogenicity study, VAF/Plus Sprague-Dawley derived Crl:CD IGS BR rats received oral doses of VX-770 at 5, 15, and 50 mg/kg/day. Vehicle control groups (0.5% w/v methylcellulose with 0.5% w/v sodium lauryl sulfate in water) with and without 0.01% simethicone were also included in the study. Rats were treated with test article or vehicle control for 89-96 weeks. Early termination of study groups due to high mortality was based upon recommendations provided to the sponsor after consultation with the ECAC (see nonclinical review submitted to IND 74,633 and dated November 5, 2010). No statistically significant test article-related tumor findings were observed. Males dosed at 50 mg/kg/day had

statistically significant lower survival in comparison to controls (with simethicone). Body weight and body weight gain were statistically significantly decreased in high-dose males at Weeks 25, 53, 77, and 89 (end of dosing) and in high-dose females at Weeks 53, 77, and 89 (end of dosing) versus controls (with simethicone). Accumulation of VX-770 and metabolites M1 and M6 was observed in males and females by Months 6 and 12.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms.

Mouse:

- The Committee concurred that the study was acceptable
- The Committee concurred that there were no drug-related neoplasms.

The committee concurred that coverage of the metabolites and the parent was acceptable.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

/NDA 203-188 Division File, DPARP
/TRobison, DPARP
/MWood, DPARP
/MRaggio, DPARP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
12/21/2011

DAVID JACOBSON KRAM
12/21/2011

included PARs, which are quite wide, in the PDR. See discussion below under tablet compression for an issue in the batch records regarding the NOR and PAR.

The finished DP (tablet) is manufactured at:

(b) (4)

The applicant provided data regarding potency adjustment by

The target potency of the tablet of (b) (4)% is achieved by

(b) (4)

Possible inspection Issue 1: There are instructions in the MBR to take samples from ten locations (b) (4) but there is no information about what is being tested or how the results of the testing are used.

(b) (4)

Possible inspection Issue 2: In the EBR (June 2009), the upper limit for the hardness is (b) (4) well within the NOR of (b) (4). However the EBR (2011) has the upper limit for hardness at (b) (4) (the PAR), (b) (4)

Possible inspection Issue 3: Samples are taken for disintegration and dissolution testing

(b) (4)
(b) (4) *There is no information on what is done with these results.*

Possible inspection Issue 4: In the MBR there are directions for taking samples for testing (b) (4) (b) (4) There is no information concerning the use of this information. The sequence of events is not clear.

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/s/

ARTHUR B SHAW
12/16/2011

PRASAD PERI
12/16/2011
I concur



NDA 203188

FILING COMMUNICATION

Vertex Pharmaceuticals, Inc.
130 Waverly Street
Cambridge, MA 12139-4242

Attention: Mark DeRosch, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. DeRosch:

Please refer to your New Drug Application (NDA) dated October 18, 2011, received October 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ivacaftor (VX-770) 150mg tablets.

We also refer to your amendments dated October 20, November 4 and 16, and December 5, 2011.

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 April 18, 2012.

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, midcycle, 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 March 28, 2012.

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

Chemistry, Manufacturing, and Controls

1. The information to support the qualification of reagents and solvents used in the synthesis of ivacaftor is insufficient.
2. There is no description of the test(s) used as in-process controls for (b) (4) during the preparation of the drug substance.
3. (b) (4)
4. There is insufficient information to evaluate your proposal to submit a change in the (b) (4) as a Level 1 change.
5. There is inadequate data to support the safety of the container-closure components.

Biopharmaceutics

6. Insufficient data have been provided to assess the suitability of the proposed dissolution acceptance criterion (Q (b) (4) % in 20 mins), including data which demonstrated satisfactory discriminating power.
7. Inadequate information has been provided to support your proposal (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.

Additionally, we request that you submit the following information:

Chemistry, Manufacturing, and Controls

1. Regarding the drug substance:
 - a. Provide the specifications (tests, analytical procedures, and acceptance criteria) for the reagents and solvents used in the synthesis of ivacaftor.
 - b. Provide test procedure(s) used as in-process controls for (b) (4)
 - c. Amend the Specification to include test and acceptance criterion for (b) (4)
 - d. Provide batch analyses for the commercial batches reporting levels of residual amounts of (b) (4)

2. In support your proposal (3.2.P.2.3 Page 6) to handle changes to (b) (4), confirm that the configuration and operating principles of the (b) (4) are similar and will result in comparable (b) (4) characteristics.

3. Regarding the Container Closure System:

Provide information to establish that the packaging component(s) and material(s) are safe under the conditions of their intended use. This information can include citations of appropriate food additive regulations and/or the results of appropriate USP test. See MAPP 5015.5 CMC Reviews of Type III DMFs for Packaging Materials <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM205259.pdf>

4. Typically, validation protocols are not submitted within the application, since the application is not the appropriate location for such protocols. The actual protocols, acceptance criteria and study outcomes would be evaluated during an inspection. It is the sponsor's responsibility to conduct all studies necessary to assure the commercial manufacturing process is capable of consistently delivering high quality product. Therefore, during the course of the review we cannot assess the process validation information (including process qualification and continued process verification) that is provided in section 3.2.P.2.3.1.6 of the NDA.

Biopharmaceutics

5. Provide the following information/data to support your proposed dissolution method and acceptance criterion:
 - a. The dissolution method report including dissolution data (individual, mean, SD, profiles) collected during the development and validation. Include data to support the discriminating power of the method (e.g. dissolution profiles showing that dissolution is able to reject tablets produced outside the targeted tablet hardness).
 - b. Complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value). Alternately tighten your proposed dissolution acceptance criterion to reflect the data.
6. Insufficient data has been provided to support your proposal (b) (4). Either include testing for (b) (4) for all batches, both for release and for stability or provide data to support your time point selection in the construction of the model to build a correlation between dissolution (b) (4). Alternatively, you may consider submitting your proposal of using dissolution as (b) (4) in a post approval setting.

Clinical Pharmacology

6. Submit the NONMEM control streams as .txt files.

LABELING

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

General

1. Spell out the words for “CFTR” when used in the label for the first time.

Highlights

Full Prescribing Information

2. Indications and Usage
 - a. Insert a “Limitations of Use” subheading to note that Kalydeco has been shown to be effective only in patients with cystic fibrosis who have a G551D mutation in the CFTR gene and that it is not effective in patients with cystic fibrosis who are homozygous for the F508 mutation in the CFTR.
 - b. Insert a statement indicating that an FDA-approved test should be used to identify the presence of the G551D mutation.

3. Adverse Reactions

Section 6.1, Clinical Trials Experience

- a. The title of Table 1 should be changed to “Adverse Reactions Reported in $\geq 5\%$ of Patients Treated with Kalydeco 150 mg Twice Daily and Greater than Placebo in Placebo-controlled Trials of 48 Weeks Duration” and the safety data represented in this table must be revised to include such information.
- b. The composite term “upper respiratory tract infection events” used in Table 1 should be “ungrouped” to include the appropriate preferred term, e.g., nasal congestion, rhinitis, nasopharyngitis, etc.
- c. Immediately following Table 1, include a section listing, by system-organ-class, adverse reactions that occurred in the Kalydeco group at a frequency of 1-5% where rates exceeded that in placebo group.

Section 6.2, Description of Selected Adverse Drug Reactions

- a. This section is reserved for post-marketing adverse reaction information. Since Kalydeco has not been yet marketed, Section 6.2 should be deleted. Information on respiratory tract infections and rash in the Current Section 6.2 are already presented in Section 6.1. Transaminase elevations should be included in Section 6.1 as well.

4. Special Populations

Section 8.9, Use of Kalydeco in Patients with Other Mutations in the CFTR Gene

(b) (4)

5. Clinical Pharmacology

Section 12.2, Pharmacodynamics

- a. As change in sweat chloride is a pharmacodynamic endpoint, the data demonstrating the effect of Kalydeco on sweat chloride should be described in the Pharmacodynamic section. The second sentence in this section which states

(b) (4)

Section 12.3, Pharmacokinetics

- b. Forest plots are generally used to capture changes in observed PK data as a result of intrinsic and extrinsic factors from in vivo studies. Therefore, (b) (4) data should be deleted from Figure 2

6. Clinical Studies

Section 14

- a. In this section studies should be described with regard to mutation in the CFTR gene rather than by specific study. For instance, Section 14.1 would describe "Studies in Patients with a G551D Mutation in the CFTR Gene". Section 14.2 should subsequently be titled as "Study in Patients Homozygous for the F508 Deletion in the CFTR Gene". The efficacy results currently described in Section 14.2 should be incorporated into Section 14.1.

(b) (4)

- b. Section 14.2, Figure 4, was not a primary or secondary endpoint in any Phase 3 trial and should be deleted. A statement stating that (b) (4)
- c. Section 14.3, Figure 5 adds no efficacy information not already presented in Figure 1 and therefore should be deleted.

We request that you resubmit labeling that addresses these labeling issues by December 23, 2011. The resubmitted labeling will be used for further labeling discussions.

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.

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 of your orphan status designation, you are exempt from this requirement.

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

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
12/14/2011



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

FACSIMILE CORRESPONDENCE

Date: November 10, 2011

To: Mark DeRosch
Senior Director, Regulatory Affairs

Company: Vertex Pharmaceuticals, Inc.
Phone: 617-444-6765

Secure Email: Mark_DeRosch@vrtx.com

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products

Phone: 301-796-2109

Subject: NDA 203188 Clinical IR # 1: r/t CRO

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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NDA 203188

Your submission dated October 18, 2011, to NDA 203188, is currently under review. We have the following request for information:

We note that the CRO, [REDACTED] (b) (4) was contracted to assist with data management for your Phase 3 program. Please clarify the role and responsibility this CRO had with regard to data collection and management for the clinical trials.

Submit a response via email to Miranda.Raggio@fda.hhs.gov by noon on Wednesday, November 16, 2011. This information will also need to subsequently be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 203188

Drafted by Miranda Raggio/11-10-11

Initialed by Sandy Barnes/ 11-10-11

Joan Buenconsejo/11-10-11

Tony Durmowicz/11-10-11

Finalized by Miranda Raggio/11-10-11

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/s/

MIRANDA B RAGGIO
11/10/2011

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division: DRH/ OIVD/ DIHD

Mail Code: HF

Consulting Reviewer Name: Maria M. Chan, PhD

Building/Room #:

Phone #: 301-796-5482

Fax #:

Email Address: maria.chan@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: DPARP

Mail Code: HF570

Requesting Reviewer Name: Kim Witzmann, M.D.

Building/Room #: 22/3341

Phone #: 301-796-5266

Fax #: 301-796-9728

Email Address: Kimberly.Witzmann@fda.hhs.gov

RPM/CSO Name and Mail Code: Miranda Raggio 796-2109

Requesting Reviewer's Concurring

Supervisor's Name: Tony Durmowicz, M.D., Clinical Team

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 11-01-11

Requested Completion Date: 12-30-2011

Submission/Application Number: NDA203188
(Not Barcode Number)

Submission Type: Original NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: October 18, 2011

Official Submission Due Date: PDUFA April 18, 2011

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

EDR link to submission: \\CDSESUB1\EVSPROD\NDA203188\203188.enxcharacters max)

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Vertex has submitted NDA# 203,188 for ivacaftor for treatment of cystic fibrosis in those with a G551D CFTR mutation. In your Pre-IDE Memorandum communication to the Sponsor on 7/29/2011, in your response to Question 1 from Vertex you noted it was acceptable to use 510(k)-cleared CF genotyping kits for identification of the G551D mutation. While DPARP agrees with your view on the use of FDA-approved genetic tests to identify the G551D mutation, Vertex has not included any reference to any type of genetic test in the proposed product label. We therefore have the following questions:

1. Should any specific reference to the types of genetic testing for the G551D mutation be included in the product label?
2. If you feel that specific reference to the types of genetic test to be used should be included in the product label, would gene sequencing be acceptable in lieu of an FDA-approved test?

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/s/

MIRANDA B RAGGIO
11/04/2011

REQUEST FOR CONSULTATION

TO (Office/Division): QT-IRT, Attention : Kozeli, Devi

FROM (Name, Office/Division, and Phone Number of Requestor): Miranda Raggio, RPM, DPARP, 301-796-2109

DATE
10-27-11

IND NO.

NDA NO.
203188

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
10-18-11

NAME OF DRUG
Ivacaftor (VX-770)

PRIORITY CONSIDERATION
YES

CLASSIFICATION OF DRUG
Respiratory

DESIRED COMPLETION DATE
January 15, 2011

NAME OF FIRM: Vertex Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: EDR link to submission: \\CDSESUB1\EVSPROD\NDA203188\203188.enx

Please review clinical report for study VX09-770-008 (Module 5.3.4.1)(TQT study).

SIGNATURE OF REQUESTOR
Miranda Raggio per Partha Roy request; cleared by S. Barnes 10-27-11

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

MIRANDA B RAGGIO
10/27/2011

SIGNATURE OF REQUESTER Miranda Raggio/Cleared by Sandy Barnes 10-21-11	METHOD OF DELIVERY (Check one) DARRTS <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

MIRANDA B RAGGIO
10/21/2011

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: Roberta Szydlo

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Miranda Raggio, RPM
DPARP, 301-796-2109

REQUEST DATE
10-20-11

IND NO.

NDA/BLA NO.
203188

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)
Original NDA

NAME OF DRUG
Ivacaftor (VX-770)

PRIORITY CONSIDERATION
Yes, Priority

CLASSIFICATION OF DRUG
Respiratory, Class I

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
March 14, 2012

NAME OF FIRM:

Vertex Pharmaceuticals, Inc.

PDUFA Date: 4-18-2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission: <\\CDSESUB1\EVSPROD\NDA203188\203188.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date] 1-17-12

Labeling Meetings: [Insert Dates] 2-29-12, 2-12-12

Wrap-Up Meeting: [Insert Date] 3-19-12

SIGNATURE OF REQUESTER

Miranda Raggio, DPARP, 6-2109.Clearead by Sandy Barnes 10-21-11

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one) DARRTS

eMAIL

HAND

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/s/

MIRANDA B RAGGIO
10/21/2011



NDA 203188

NDA ACKNOWLEDGMENT

Vertex Pharmaceuticals, Inc.
130 Waverly Street
Cambridge, MA 12139-4242

Attention: Mark DeRosch, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. DeRosch:

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 150mg tablets

Date of Application: October 18, 2011

Date of Receipt: October 18, 2011

Our Reference Number: NDA 203188

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 December 17, 2011, 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). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA # 203188** submitted on October 18, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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>.

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Miranda Raggio, RN, BSN, MA
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/

MIRANDA B RAGGIO
10/20/2011