

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201917Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201-917

SUPPL # Original NDA Submission

HFD#530

Trade Name INCIVEK

Generic Name Telaprevir

Applicant Name Vertex Pharmaceuticals, Inc.

Approval Date, If Known May 23, 2011

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?

5 years

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: Myung-Joo Patricia Hong, M.S.

Title: Regulatory Project Manager

Date: April 12, 2011

Name of Office/Division Director signing form: Jeffrey Murray, M.D.

Title: Deputy Division Director

Division of Antiviral Products

Office of Antimicrobial Products

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/

MYUNG JOO P HONG
04/12/2011

JEFFREY S MURRAY
04/19/2011

1 REQUEST FOR DEFERRAL

A deferral is being requested for studies of telaprevir in children aged 3 to less than 18 years for the indication of treatment of genotype 1 chronic hepatitis C virus (HCV infection).

Telaprevir in combination with Peg-IFN and RBV is indicated for the treatment of children and adolescents 3 to less than 18 years of age with genotype 1 chronic HCV infection.

A waiver has been requested for children less than 3 years of age (Module 1.9.1).

A pediatric plan was submitted electronically to the Agency in IND 71,832; Sequence 295 Module 1.9.6 on 23 February 2009. At the time of this writing, Vertex is reviewing comments from the Agency in anticipation of a Written Request.

2 REASONS FOR REQUESTING A DEFERRAL OF PEDIATRIC STUDIES

The adult studies of telaprevir in adults have been completed, are included in this submission, and are ready for review.

A thorough evaluation of the benefit-risk profile of telaprevir is warranted prior to the initiation of studies of telaprevir in the pediatric population. Such an evaluation will help determine the appropriateness of conducting a trial in subjects under age 18 who have chronic hepatitis C, and will provide important information about the need for any additional safety monitoring in this population.

In 2008, the EMEA adopted a positive opinion on the pediatric investigational plan (PIP) for telaprevir, which included the proposed Phase 2 pediatric study design. Because of the need to establish benefit-risk in adults prior to initiating the pediatric studies, the Phase 2 protocol will be further discussed with FDA and EMEA/PDCO after the reports of the Phase 3 adult studies are assessed by the regulatory agencies. These Phase 3 study reports (VX07-950-108, VX07-950-111 and VX-950-TiDP24-C216) are included in NDA 201917.

The tentative timelines for the conduct of clinical studies and subsequent sNDA are presented in Table 1.

Table 1 Predicted Timelines for Completion of Studies Relevant to Pediatric Development Applications Related to Pediatrics

Step in Development or Study	Age Group	Status	Initiation Date	Completion Date	Predicted Timing of Planned sNDA Submission
(b) (4)					

Table 1 Predicted Timelines for Completion of Studies Relevant to Pediatric Development Applications Related to Pediatrics

Step in Development or Study	Age Group	Status	Initiation Date	Completion Date	Predicted Timing of Planned sNDA Submission
Clinical¹				(b) (4)	
Relative bioavailability of pediatric formulation	adults	planned			2014
Phase 2 safety, pharmacokinetics, and efficacy in HCV-infected children	3 years to <18 years	planned			2014

1: Pediatric Plan Table 7.3 in IND 71,832; Sequence 295

3 CERTIFICATION

Vertex Pharmaceuticals Incorporated hereby certifies that the information contained in this Request for Deferral of Pediatric Studies is accurate and complete at this time.

1 REQUEST FOR WAIVER

A waiver is requested for the study of telaprevir (VX-950) in the pediatric population 0 to less than 3 years of age for the indication of treatment of chronic hepatitis C virus (HCV) infection.

Grounds for Waiver for Pediatric Population Less Than 3 Years of Age

1. Necessary studies are impossible or highly impracticable. Clinical trials in pediatric patients <3 years of age are not considered feasible due to the small proportion of patients in this age group requiring treatment for chronic hepatitis C (CHC) and due to the lack of a stable liquid formulation suitable for this age group.
2. Neither peginterferon alfa (Peg-IFN-alfa) nor ribavirin (RBV), with which telaprevir is being developed in combination, is approved for use in this age group. Non-pegylated IFN is also not approved for use in this age group.
3. Diagnosis of CHC cannot be made until at least 18 to 24 months of age for the following reasons:

There are no clear guidelines for the screening and diagnosis of chronic HCV infection in children. The utility of anti-HCV antibody detection in infants born to HCV-infected mothers is limited during the first months of life because all of the infants acquire passive antibodies. Passively acquired antibodies may persist past the first year of life. HCV-infected infants may clear the virus spontaneously,^{1,2,3-6} and transient HCV infection with multiple positive HCV RNA results and later clearance of virus is possible, depending on the timing and frequency of HCV testing.

Testing of infants for HCV is generally considered unnecessary until the child reaches 1 year of age, at which time a qualitative HCV RNA detection should be performed.⁷ If the result is positive, testing should be repeated when the child is 18 to 24 months of age.⁷ If confirmed positive at that time, the child likely has a chronic infection.^{5,7,8} Chronic persistent infection has also been defined as having a positive HCV RNA for a duration of >2 years in infants, and for >6 months in children >2 years of age.⁸

2 CERTIFICATION

Request for Waiver to Study Patients 0 to Less Than 3 years of age

Based on a review of the available literature, Vertex Pharmaceuticals Incorporated certifies that the rationale presented above supports the request for a waiver of this type.

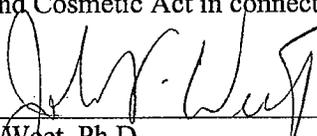
3 REFERENCES

1. Vogt M, Lang T, Frosner G, Klingler C, Sendl AF, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999;341(12):866-70.

2. Jara P, Resti M, Hierro L, Giacchino R, Barbera C, Zancan L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003;36(3):275-80.
3. Ceci O, Margiotta M, Mareello F, Francavilla R, Loizzi P, Francavilla A, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. *J Pediatr Gastroenterol Nutr* 2001;33(5):570-5.
4. Yeung LT, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. *J Viral Hepat* 2007;14(11):797-805.
5. Resti M, Jara P, Hierro L, Azzari C, Giacchino R, Zuin G, et al. Clinical features and progression of perinatally acquired hepatitis C virus infection. *J Med Virol* 2003;70(3):373-7.
6. The European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis* 2005;41(1):45-51.
7. Slowik MK, Jhaveri R. Hepatitis B and C viruses in infants and young children. *Semin Pediatr Infect Dis* 2005;16(4):296-305.
8. Kelly D. Viral hepatitis B and C in children. *J R Soc Med* 2006;99(7):353-7.

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.



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

Date July 14, 2010

Confidential

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 201-917 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Incivek™ Established/Proper Name: Telaprevir Dosage Form: 375 mg Film-Coated Tablets		Applicant: Vertex Pharmaceuticals, Inc. Agent for Applicant (if applicable): John Weet, Ph.D.
RPM: Myung-Joo Patricia Hong, M.S.		Division: DAVP
<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>May 23, 2011</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 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 checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input 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 checked="" 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 checked="" 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 checked="" 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	May 23, 2011
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) AP - May 23, 2011
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. 	May 20, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	November 22, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

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

❖ 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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input 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. 	May 20, 2011
<ul style="list-style-type: none"> Original applicant-proposed labeling 	November 22, 2010
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ 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 	May 20, 2011
❖ 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>) 	Acceptability letter - 4/29/11 Review Memo - 4/29/11
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 5/23/11 <input checked="" type="checkbox"/> DMEPA 5/4/11, 5/20/11 <input checked="" type="checkbox"/> DRISK 4/25/11, 5/18/11 <input checked="" type="checkbox"/> DDMAC 5/20/11 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	January 11, 2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>February 9, 2011</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ 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>)	Pre-Submission-7/21/10, 9/28/10, 11/8/10

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

	Full Submission - 12/3/10, 12/10/10, 12/13/10, 12/15/10, 12/16/10, 12/22/10, 1/5/11, 1/6/11, 1/10/11, 1/11/11, 1/12/11, 1/21/11, 1/24/11, 1/25/11, 1/27/11, 2/4/11, 2/14/11, 2/15/11, 2/16/11, 2/18/11, 2/24/11, 3/1/11, 3/2/11, 3/3/11, 3/4/11, 3/9/11, 3/10/11, 3/11/11, 3/14/11, 3/16/11, 3/17/11, 3/18/11, 3/21/11, 3/24/11, 3/25/11, 3/28/11, 3/31/11, 4/6/11, 4/8/11, 4/11/11, 4/13/11, 4/14/11, 4/15/11, 4/19/11, 4/20/11, 4/25/11, 4/27/11, 4/29/11, 5/3/11, 5/4/11, 5/5/11, 5/6/11, 5/11/11, 5/12/11, 5/13/11, 5/18/11, 5/19/11, 5/20/11
❖ Internal memoranda, telecons, etc.	3/16/11(entered 4-4-11), 5/20/11 (entered 5-23-11)
❖ 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 September 28, 2010
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg March 19, 2008 (CMC Meeting)
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	April 28, 2011
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	May 5, 2011
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None AP - May 23, 2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None AP - May 13, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None AP - May 2, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 9
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>)	AP - April 22, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input 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>)	Under clinical review memo, page 13

⁵ Filing reviews should be filed with the discipline reviews.

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None AP - 4/15/11
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None AP - 4/25/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None AP - 4/22/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ 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 AP - 5/23/11
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Biopharmaceutics: AP - 4/20/11 Quality (Combined): AP - 4/25/11 Quality (2 nd Review): AP - 5/20/11
❖ 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 Statistics: M. Shen AP - 4/12/11
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Acceptable - 4/25/11
<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 checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 5/9/11 <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</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

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.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review)

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.

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/s/

MYUNG JOO P HONG
05/24/2011



**MEMORANDUM OF MEETING MINUTES
(INTERNAL)**

MEETING DATE: May 20, 2011
TIME: 12 - 12:30 pm
LOCATION: White Oak Conference Room 6396
APPLICATION: NDA 201917
DRUG NAME: Telaprevir
TYPE OF MEETING: Advice for Expedited Safety Reporting after Approval

FDA ATTENDEES:

Debra Birnkrant, M.D., Division Director
Linda Lewis, M.D., Clinical Team Leader
Russ Fleischer, PA-C, MPH, Clinical Reviewer
Kendall Marcus, M.D., Safety Deputy Director
Vicky Tyson, Chief Project Manager
Patricia Hong, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Vertex Pharmaceutical, Inc.

Chuck Miller, Director, Regulatory Affairs
Juergen Froehlich, VP Regulatory Affairs
Jack Weet, VP Regulatory Affairs
Henry Seto, VP Global Patient Safety
Priya Singhal, Senior Director Global Patient Safety
Elena Koundourakis, VP Regulatory Affairs

BACKGROUND:

This teleconference was held to ask Vertex to submit expedited safety reports for all serious skin reactions that occur after approval of telaprevir.

DISCUSSION:

DAVP opened the discussion by stating that although expedited reports are usually only required for serious and unexpected adverse events, Vertex should submit expedited reports for any serious skin reactions that require hospitalization, cause a disability or death. This request is being made because of the potential for the SAEs, SJS, TEN and DRESS with the use of telaprevir combination therapy. Expedited reports should be submitted for all serious skin reactions from ongoing clinical trials and spontaneous post approval events. These reports should be submitted in real time as

single case reports, in addition to being submitted in the quarterly periodic adverse event reports (PADERS) as required under the regulations. Vertex acknowledged these recommendations, confirmed that they will follow DAVP's advice and asked how long they have to submit expedited reports of all serious skin reactions. DAVP will have to review the reports, the types of events and frequency to determine how long this requirement will be in place.

DAVP informed Vertex that a few more revisions, regarding mild rash that can become severe and require hospitalization, have been made to the Medication Guide and will be sent to them shortly after the teleconference.

Vertex submitted promotional materials and a draft of the press release and asked if DAVP will have any comments on the draft of the press release. Dr. Birnkrant responded, the review team is reviewing the draft and FDA usually doesn't provide comments on press release material unless the document contains information that is promotional. DAVP will let Vertex know once the review team has completed their review, if there are no additional comments or concerns.

DAVP informed Vertex that we will finalize everything today but do not take an action until the PDUFA goal date, May 23, 2011.

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/s/

MYUNG JOO P HONG
05/23/2011

From: Chuck_Miller@vrtx.com
Sent: Wednesday, May 18, 2011 12:06 PM
To: Hong, Myung-Joo P.
Subject: Re: Telaprevir PREA PMR

Hi Pat,

We love the new language!!

We accept it without further comment.

From: "Hong, Myung-Joo P." [Myung-Joo.Hong@fda.hhs.gov]
Sent: 05/18/2011 11:54 AM AST
To: Chuck Miller
Subject: Telaprevir PREA PMR

Hi chuck, we are revising the wording for your required pediatric assessment (1771-1) to read:

"Conduct a pharmacokinetics trial (or subtrial) of telaprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine appropriate dosing for children that will result in exposures similar to those found to be safe and effective in adults."

The reason for this change is to allow for flexibility in future pediatric study design(s). Due to telaprevir's time-dependent PK characteristics and the effect of Peg-IFN/RBV on telaprevir exposure following multiple doses, matching exposures in pediatric patients following a single-dose of telaprevir may not fully capture these effects. Please note that the change in wording does not preclude the possibility of a single-dose study; however, discussion and further justification may be warranted to substantiate a single-dose PK trial.

Would you confirm your acceptance for this change?

Thanks,
Pat

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/s/

MYUNG JOO P HONG
05/18/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 18, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 18, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have reviewed the revised container labels and blister labels submitted on May 17, 2011 and we have the following comments from the review team:

Carton and Container Labels

1. Please revise the presentation of the established name on all carton labeling and container and blister labels to ensure it is at least 1/2 the size of the proprietary name taking into consideration all of the requirements in 21 CFR 201.10(g)(2): *The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.*
2. Increase the prominence of the dosage form and strength statements on all carton labeling and container labels. As currently presented it is small and lacks prominence.

Please provide your response by May 19, 2011.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

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/s/

MYUNG JOO P HONG
05/18/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 13, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 13, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team. Please provide your response by **May 16, 2011**.

Carton Labeling and Container Labels

1. Relocate the presentation of the strength statement on the bottle label and the monthly and weekly carton labeling to appear in the following sequence:

INCIVEK
(telaprevir)
Tablets
375 mg

2. Revise the statement, “with food (not low-fat)” to read, “with a meal or snack (containing approximately 20 grams of fat)” on the carton labeling below the food pictogram and blister label which is consistent with the presentation of the statement in the package insert labeling.

Clinical Virology

DAVP's comments are in italics under each section.

12.4 MICROBIOLOGY

Resistance
In Cell Culture

- We modified the first sentence to state that resistant replicons could be selected in cell culture. We added additional phenotypic data for relevant substitutions in this section.

- We removed the sentence

(b) (4)

(b) (4)

In Clinical Studies

- We removed the statements

(b) (4)

(b) (4)

- We removed the statement

(b) (4)

(b) (4)

Table 8

- We agree to add V36L, T54S, R155T and A156 rows to table. However, we do not agree to remove V36M and R155K individual counts from V36M+R155K, because there are so many different combinations of 2 or 3 resistant-associated substitutions that this becomes very difficult to interpret. Rather we have added footnotes to Table 8 to clarify:
¹Alone or in combination with other substitutions (includes mixtures)
²Subjects with this combination are also encompassed in two V36M and R155K rows above.
- In Table 8, we have updated % and numbers to include all subjects with the indicated substitution including mixtures at this position.

For the last row with multiple substitutions listed, (b) (4) is not consistent with our analysis. Changed to “Less than 2%.”

Persistence of Resistance-Associated Substitutions

- We agree to the changes in this section.
- We have added the sentence “No data are available regarding INCIVEK efficacy among subjects who were previously exposed to INCIVEK, or who previously failed treatment with a INCIVEK-containing regimen.”

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

- *We accept these changes, but are keeping D168 as D168E was present in 8 subjects at baseline.*

Cross-Resistance

- *We accept these changes with minor modifications.*

Subject IDs of NO SVR24 Subset with Any Emergent Substitution at V36, T54, R155, A156 or D168

VX07-950-108-104-104005 1a
 VX07-950-108-106-106006 1a
 VX07-950-108-108-108008 1a
 VX07-950-108-110-110007 1a
 VX07-950-108-111-111002 1a
 VX07-950-108-113-113002 1a
 VX07-950-108-113-113015 1a
 VX07-950-108-114-114008 1a
 VX07-950-108-117-117005 1b
 VX07-950-108-118-118004 1a
 VX07-950-108-118-118007 1a
 VX07-950-108-119-119002 1a
 VX07-950-108-119-119005 1a
 VX07-950-108-119-119006 1b
 VX07-950-108-119-119008 1a
 VX07-950-108-119-119009 1a
 VX07-950-108-120-120004 1a
 VX07-950-108-121-121004 1a
 VX07-950-108-121-121008 1a
 VX07-950-108-122-122001 1a
 VX07-950-108-124-124014 1a
 VX07-950-108-125-125003 1a
 VX07-950-108-125-125009 1a
 VX07-950-108-126-126002 1a
 VX07-950-108-128-128008 1a
 VX07-950-108-128-128010 1b
 VX07-950-108-129-129004 1a
 VX07-950-108-129-129006 1a
 VX07-950-108-129-129012 1b
 VX07-950-108-130-130003 1a
 VX07-950-108-130-130004 1a
 VX07-950-108-133-133003 1a
 VX07-950-108-135-135002 1a
 VX07-950-108-137-137004 1a
 VX07-950-108-139-139005 1b
 VX07-950-108-140-140004 1a
 VX07-950-108-140-140006 1a

VX07-950-108-140-140008 1a
VX07-950-108-143-143003 1a
VX07-950-108-143-143006 1a
VX07-950-108-144-144006 1a
VX07-950-108-144-144008 1a
VX07-950-108-145-145010 1a
VX07-950-108-149-149005 1a
VX07-950-108-149-149011 1a
VX07-950-108-149-149015 1b
VX07-950-108-150-150001 1a
VX07-950-108-151-151003 1a
VX07-950-108-151-151006 1b
VX07-950-108-151-151017 1a
VX07-950-108-152-152004 1a
VX07-950-108-156-156005 1b
VX07-950-108-157-157005 1a
VX07-950-108-158-158010 1b
VX07-950-108-160-160003 1a
VX07-950-108-160-160008 1a
VX07-950-108-161-161005 1a
VX07-950-108-162-162005 1a
VX07-950-108-164-164003 1a
VX07-950-108-165-165001 1a
VX07-950-108-166-166006 1a
VX07-950-108-166-166007 1a
VX07-950-108-169-169007 1a
VX07-950-108-169-169016 1a
VX07-950-108-169-169024 1b
VX07-950-108-173-173003 1b
VX07-950-108-173-173004 1a
VX07-950-108-173-173009 1a
VX07-950-108-180-180002 1a
VX07-950-108-181-181004 1b
VX07-950-108-184-184007 1a
VX07-950-108-201-201008 1b
VX07-950-108-202-202006 1a
VX07-950-108-205-205007 1a
VX07-950-108-205-205009 1a
VX07-950-108-206-206007 1a
VX07-950-108-207-207003 1b
VX07-950-108-211-211008 1a
VX07-950-108-213-213003 1b
VX07-950-108-214-214002 1b
VX07-950-108-301-301002 1a
VX07-950-108-303-303003 1a
VX07-950-108-305-305006 1b

VX07-950-108-305-305008 1a
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Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

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/s/

MYUNG JOO P HONG
05/13/2011



ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 12, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: PMR comment

Please refer to your November 23, 2010, telaprevir NDA 201-917. The DAVP is proposing the following clinical pharmacology postmarketing requirement (PMR). Please propose timelines and provide your response by **May 13, 2011**.

Clinical Pharmacology PMR

- 1. Conduct a PK study in subjects with end-stage renal disease (ESRD) on intermittent hemodialysis (HD) to determine the effect of HD on telaprevir exposure, in order to provide dosing recommendations for HCV patients on HD.**

Protocol Submission:
Study Completion:
Study Report Submission:

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Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

MYUNG JOO P HONG
05/12/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, May 11, 2011 1:04 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Labeling Comment

Hi Chuck, additional request for information:

- Please provide any informational material or instruction sheets that were given to subjects in Studies 111, C216, and 108 regarding intake of food with telaprevir dosing. If the wording is different between trials, please provide the material for each trial.

Thanks,
Pat

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/s/

MYUNG JOO P HONG
05/11/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 11, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 11, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: PMRs/PMCs comments

Please refer to your November 23, 2010 submission submitted to NDA 201-917. The DAVP is proposing the following postmarketing commitments (PMCs) and requirements (PMRs). Please provide your responses to these requests by **May 13, 2011**.

PREA PMRs

- 1. Conduct a (b) (4) pharmacokinetics study (or substudy) of telaprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine appropriate dosing for children that will result in exposures similar to those found to be safe and effective in adults.**

Protocol Submission: September, 2011
Study Completion: June, 2014
Study Report Submission: October, 2014

- 2. Conduct a trial to evaluate safety and treatment response of telaprevir in combination with pegylated interferon and ribavirin as measured by sustained virologic response (SVR) in pediatric subjects 3 through 17 years of age, including previously untreated subjects and those who have failed a prior course of pegylated interferon and ribavirin therapy. This trial should include at least 5 years follow-up of pediatric subjects to characterize long term safety of telaprevir, including growth assessment and sexual maturation in pediatric subjects, determination of durability of response, and characterization of telaprevir resistance-associated substitutions.**

Protocol Submission: (b) (4)
Study Completion: (b) (4)
Study Report Submission (without long-term follow-up): (b) (4)
[Study Report Submission of Long-Term Safety Follow-Up:](#) (b) (4)

Clinical PMCs

3. **Conduct a trial to evaluate safety and treatment response among Blacks/African Americans compared to non-Blacks/African Americans.**

Protocol Submission: September, 2011
Study Completion Date: (b) (4)
Study Report Submission: (b) (4)

4. **Conduct a trial to evaluate safety and treatment response among treatment naïve and experienced subjects with cirrhosis compared to subjects without cirrhosis.**

Protocol Submission: September, 2011
Study Completion Date: (b) (4)
Study Report Submission: (b) (4)

5. **Conduct a trial (VX11-950-115) to evaluate safety and treatment responses among treatment naïve and experienced HIV/HCV co-infected subjects.**

Protocol Submission: January, 2012
Study Completion date: June, 2014
Study Report submission: December, 2014

Pharmacogenomics PMCs

- 6.



Clinical Virology PMRs

7. **Conduct a study to assess the impact of the following telaprevir treatment emergent amino acid substitutions on phenotypic susceptibility of telaprevir in the HCV replicon system.**

- I132V (genotype 1a and 1b replicon)
- K244R (genotype 1a and 1b replicon)
- K360R (genotype 1a and 1b replicon)
- R155K ± NS4A_A36V (genotype 1a)
- NS4A_E53K (genotype 1a and 1b replicon)

8. **Conduct a study to analyze a representative subset of samples from subjects who experienced virologic failure in the Phase 3 studies, but for whom no clear resistance-associated substitutions in NS3/4A were detected, for the presence of substitutions in NS3/4A protease cleavage sites.**

Please confirm your acceptance for the proposed timelines for comments 1 through 6 or propose alternate dates and provide your justification. Please propose your timeline for clinical virology PMRs.

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Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

MYUNG JOO P HONG
05/11/2011

From: Hong, Myung-Joo P.
Sent: Friday, May 06, 2011 4:30 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Labeling Proposal

Attachments: 050611 PI to Vertex.doc

Hi chuck, attached is our labeling proposal. We have made extensive recommendations in format and content of the proposed telaprevir label as noted in the Track Changes document. It is impractical to try to explain all of these changes in the document, particularly because it has been edited by several reviewers and some sections have been revised multiple times.

Few things I need to remind you:

1. Please double check the Highlights section and Table of Contents to be sure they correctly reflect the edited version. We did not align all sections. In particular, please recheck all references to other sections as subsection numbers may have changed or been eliminated.
2. In general, we use "patients" to refer to individuals who may receive telaprevir in clinical practice and "subjects" to refer to individuals who are enrolled in a clinical trial. Please confirm that these designations are correct throughout.
3. After internal discussion among our Pharmacometrics, Virology and Clinical reviewers we believe that the HCV RNA level to be used for treatment stopping rules ("futility rules") should be 1000 IU/mL [REDACTED] (b) (4). Our reviewers identified a small number of subjects with HCV RNA between 100-1000 IU/mL at the Week 4 or Week 12 timepoints who achieved SVR. Although the absolute numbers were small, the proportion of responders in this subgroup was significant. We are willing to discuss this recommendation with you via tcon if necessary.
4. We do not believe the figures you proposed for duration of treatment were useful for labeling but have tried to incorporate all duration of treatment recommendations into a table also incorporating the stopping rules.
5. Although we have not incorporated all Warnings and Precautions relevant to peginterferon and ribavirin in the telaprevir label, because it is considered a critical safety issue and may be impacted by the telaprevir/ethinyl estradiol drug-drug interaction, we have incorporated information related to the ribavirin pregnancy warning in several sections.
6. Some proposed Warnings and Precautions were not considered necessary and were deleted.

7. We have included limited IL28B substudy information in a specific Pharmacogenomics subsection.
8. The Clinical Studies section has been significantly shortened. We do not believe it is necessary to show subgroup responses that are essentially the same as for the overall study population. Blacks and cirrhotics, as relatively small but potentially different subgroups, have been highlighted in text. Also, for Study C216 we propose reorganizing the response rate table. Finally, because the data are limited and the study is on-going, Study 112 is not considered appropriate for inclusion in this section. Data from the interim analysis is included in the Microbiology section.
9. We have added several subsections to Section 17 - Patient Counseling Information as this information may be included in the Medication Guide. Some is not included elsewhere in the label.
10. We deleted tables and added tables. Due to deletion and addition of tables, the table #s have been changed. Please make all corrections necessary which are relevant to these changes. i.e., Any statement referring to specific table # needs to be updated.
11. Please write out all "greater than" or "equal to" and "less than" or "equal to" signs, if there are any remaining signs. We did some but we may missed some.

I didn't include MG since we haven't discussed yet.

Please provide your response by Tuesday (5/10/11). When you response to our request about container label/carton, you can provide mock-up copy.

Thanks,
Pat



050611 PI to
Vertex.doc (1 MB)...

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MYUNG JOO P HONG
05/06/2011

From: Hong, Myung-Joo P.
Sent: Thursday, May 05, 2011 10:51 AM
To: 'Chuck_Miller@vrtx.com'
Subject: FW: NDA 201917 Information Request

Attachments: FDA RELAPSE COMPARISON.zip; emfalert.txt

Hi Chuck, our responses are listed below in blue font.

Thanks,
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, May 04, 2011 11:45 PM
To: Hong, Myung-Joo P.
Subject: Re: NDA 201917 Information Request

Hi Pat,

we have been working through the Stats IR letter regarding relapse that you sent on 3 May. In order to create the listing using the rules outlined in the IR, we used the assumptions listed below (See Assumptions and Interpretations) for which we are seeking confirmation.

Following the FDA rules, we have created a list of discrepancies, that is, subjects for which Vertex and FDA results are not aligned. In advance of a formal submission (due by the 9th per the IR), it may be beneficial to discuss the rules included in the IR prior to finalization. Would it be possible to perhaps have a short teleconference either on Thursday (5 May) or early Friday so that our statistician and programmer can work through the details with the FDA statistician?

I am including a preliminary listing of the discrepancies (as outlined above) for each study, a SAS dataset that contains the information, as well as a SAS program (for Study 108 only, as an example) that contains the logic applied by Vertex to fulfill the IR rules. All are contained in the attached .zip file.

Assumptions and Interpretations

- In the request it is specified how the windows for the relapse analyses should be calculated. Our interpretation is that subjects who do not have any HCV RNA measurements in any of the specified windows have been excluded from the analyses. ***Please confirm.***

FDA Response: Subjects without post EOT data are excluded from numerator and denominator.

- It is our assumption that HCV RNA < 25 IU/mL is regarded as undetectable in this analysis. ***Please confirm.***

FDA Response: Yes.

- It is our assumption that if a subject has multiple HCV RNA assessments in a defined visit window the last assessment in the window will be used for the analysis. ***Please confirm.***

FDA Response: Tom thinks that is right. He doesn't remember there being any such subjects but that choice is probably the best.

- It is our assumption that a subject who has a detectable HCV RNA at W4, W12 and W24 will be considered as having relapse at W4. *Please confirm.*

FDA Response: Yes, but we mostly just want subjects counted as: 1) SVR24; 2) lost to follow up while suppressed post EOT but before week EOT+12; 3) observed to relapse after being suppressed at EOT or later; and 4) never observed suppressed at or after EOT. Group 4 is not included in the relapse rate computation.

- *Please confirm* that samples from local labs should be excluded from the relapse calculation.

FDA Response: Tom doesn't remember this coming up at all.

- *Please confirm* that for subjects who do not have a HCV RNA measurement in the EOT window the first available HCV RNA measurements from any of the W4, W12 or W24 windows will be considered as EOT.

FDA Response: Yes, first observation EOT or later is the EOT observation. However, subjects not suppressed early in EOT period but suppressed at EOT+24 or missing at EOT+24 and suppressed at EOT+12 count as suppressed EOT. They are in the denominator on relapse rates but they are not relapsers. Subjects suppressed at EOT, detectable at EOT+4 or 12, suppressed at EOT+24 are not relapsers, they are SVR24. There is one subject who was SVR24 but relapsed at week 84=EOT+48. Right now we are not counting him as a relapse. Technically we might call him a relapser but one subject isn't going to matter much.

Best regards,

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 05/03/2011 05:15 PM
Subject: NDA 201917 Information Request

Hi Chuck, our IR letter attached. I am also attaching word version of tables.

thanks,
Pat

[attachment "050311 Telaprevir.stat comments.pdf" deleted by Chuck Miller/BOS1/VRTX] [attachment "REBOUND_BY_USUBJID.doc" deleted by Chuck Miller/BOS1/VRTX] [attachment "rel_tab.doc" deleted by Chuck Miller/BOS1/VRTX]

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MYUNG JOO P HONG
05/05/2011



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 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 4, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 4, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Carton and Container Labels

1. Blister Label (2 X 375 mg)
 - a. Ensure the established name is at least ½ the size of proprietary name and has a commensurate prominence with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See 21 CFR 201.10(g)(2).
 - b. Delete the statement, ' [REDACTED] (b) (4) [REDACTED] ' to provide adequate space for implementation of the following comments:
 - 1) It is not clear to users whether the entire blister contains 375 mg. Therefore, please revise the presentation of the strength statement on each blister to read :

750 mg	OR	750 mg
(375 mg per tablet)		(2 X 375 mg tablets)
 - 2) Revise the statement, 'Take With Food', to read, 'Take With Meals', to be consistent with the statements in the package insert labeling.
2. Blister Carton Labeling (42 tablets)
 - a. See comments 1.a above.

- b. Revise the font color for the presentation of the strength statement to a darker color to provide for a better color contrast that will increase readability and prominence of the statement.
 - c. Revise the statement ‘Take with food’ presented under the food pictogram on the bottom panel to read, ‘Take with meals’ to be consistent with the statements in the package insert labeling.
 - d. Revise the statement, ‘(b) (4)’, to read, ‘Tradename must only be taken with both peginterferon alfa and ribavirin.’ As currently presented the statement is intended to prescribers and may be confusing to patients.
 - e. Delete the ‘(b) (4)’, and ‘(b) (4)’, fields. As currently presented it is unclear how these fields will be useful to patients or healthcare providers given this is a fixed dose.
3. Blister Carton Labeling (168 tablets)
- a. See comments 1.a, 2.b, and 2.d above.
 - b. Revise the statement ‘Take with food’ presented under the food pictogram on the inside of the top flap to read ‘Take with meals,’ to be consistent with the statements in the package insert labeling.
 - c. Increase the prominence (i.e., bold) of the dosing instructions, ‘Take 2 tablets three times a day (7 to 9 hours apart)’ under the tablet pictograms.
 - d. Revise the Medication Guide statement to read “ATTENTION PHARMACIST: Dispense the enclosed Medication Guide to each patient.”
4. Container Label (168 tablets) for Institutional Use:
- a. See comments 1.a and 1.b(2) above.
 - b. Ensure that the net quantity statement ‘168 tablets’ is presented away from the strength statement.
 - c. Delete the (b) (4) contained in the statement that begins (b) (4)
[REDACTED]
Please revise the statement to read ‘Each Incivek (telaprevir) tablet contains 375 mg of telaprevir.’

Please provide your response by May 9, 2011.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

MYUNG JOO P HONG
05/04/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 3, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 3, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Statistical

1. Please either recalculate the relapse rates using the algorithm listed below or discuss with us which subjects there is disagreement on with respect to relapse status from the tables attached at the end of the letter:

The denominator is anybody who is ever observed suppressed at or after EOT
Calculate windows for EOT, EOT+4, EOT+12, EOT+24 by
IF PLANN = 24 weeks THEN DO ;

IF (24<=RWEEK <= 26) THEN WINDOW = 0 ;
IF (26<RWEEK <= 32) THEN WINDOW = 4 ;
IF (32<RWEEK <= 42) THEN WINDOW = 12 ;
IF (42< RWEEK <= 56) THEN WINDOW = 24 ;
IF (56< RWEEK) THEN WINDOW = 48 ;

END ;

IF PLANN = 48 weeks THEN DO ;

IF (48<=RWEEK <= 50) THEN WINDOW = 0 ;
IF (50<RWEEK <= 56) THEN WINDOW = 4 ;
IF (56<RWEEK <= 66) THEN WINDOW = 12 ;
IF (66< RWEEK <= 80) THEN WINDOW = 24 ;
IF (80< RWEEK) THEN WINDOW = 48 ;

END ;

If HCV in window 24 is observed to be undetectable, then subject not rebounded, stop calculation for that subject.

If HCV in window 24 is observed to be detectable, then subject rebounded, stop calculation for that subject.

If HCV in window 24 is missing, then subject look at HCV in window 12.

If HCV in window 12 is observed to be undetectable, then subject not rebounded, stop calculation for that subject.

If HCV in window 12 is observed to be detectable, then subject rebounded, stop calculation for that subject.

If HCV in window 12 is missing, then subject look at HCV in window 4.

If HCV in window 4 is observed to be undetectable, then subject not rebounded, stop calculation for that subject.

If HCV in window 4 is observed to be detectable, then subject rebounded, stop calculation for that subject.

If HCV in window 4 is missing, then subject is lost to follow-up while suppressed.

There are some subjects who are undetectable at 0, detectable at 4, undetectable at 24. They are not counted as rebounders (relapsers). Undetectable at window 24 means stop the calculation and count as not rebounded.

Please provide your response by May 9, 2011.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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MYUNG JOO P HONG
05/03/2011



NDA 201917

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Vertex Pharmaceuticals, Inc.
130 Waverly Street
Cambridge, MA 02139

ATTENTION: John F. Weet, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) dated November 22, 2010, received November 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Telaprevir Tablets, 375 mg.

We also refer to your March 4, 2011, correspondence, received March 4, 2011, requesting review of your proposed proprietary name, Incivek. We have completed our review of the proposed proprietary name, Incivek, and have concluded that it is acceptable.

The proposed proprietary name, Incivek, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your March 4, 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 Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Myong-Joo P. Hong at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/29/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, April 27, 2011 7:41 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical Request

Hi Chuck, we have additional requests:

We remain concerned about the elevations in bilirubin levels, and hemolysis may only partly explain the mechanism. Please respond to the following requests ASAP:

1. For each subject with a Grade 3 and/or 4 bilirubin elevation during the T/Pbo dosing period, please provide serial total and direct bilirubin, ALT, AST, and alkaline phosphatase results by study visit.
2. Please provide whether there was a requirement that testing be performed at a shorter interval with stopping instructions if values exceeded a specified level, if biochemical abnormalities were observed?
3. Please clarify that Grade 3 abnormality represents an increase in total serum bilirubin of between 3 and 10 times the upper level of normal while Grade 4 defines a bilirubin value as greater than 10 times the upper limit? If not, please supply the values for each grade.
4. Please provide a list of concomitant drugs and/or herbal products each subject received during the T/Pbo dosing period.

Thanks,
Pat

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/s/

MYUNG JOO P HONG
04/27/2011

From: Hong, Myung-Joo P.
Sent: Monday, April 25, 2011 5:09 PM
To: 'Chuck_Miller@vrtx.com'
Subject: AC meeting Request

Hi Chuck, Russ found that 50% of telaprevir subjects had direct bilirubin levels above normal limits compare to 16 % of pbo/PR. Please tell if you had similar findings and please provide possible explanations for potential mechanism. Please provide us the timing of these elevations, height of elevations, and persistence of elevations. Please provide your responses by NOON tomorrow.

Thanks
Pat

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/s/

MYUNG JOO P HONG
04/25/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, April 20, 2011 10:19 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical Request

Hi Chuck, please submit the SAS file as suggested below.

thanks,
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, April 20, 2011 4:59 PM
To: Hong, Myung-Joo P.
Subject: Re: Telaprevir Clinical Request

Hi Pat,

For number 1 below, I now could send you a SAS dataset containing the following variables if that makes adjudication easier:

Unique Subject Identifier
Subject Identifier
Full Analysis Set Population Flag
Planned Treatment
Planned Treatment Number
Achieve SVR24 (Snapshot)
Achieve SVR24 (Snapshot), num

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 04/19/2011 04:59 PM
Subject: Telaprevir Clinical Request

Hi Chuck, additional requests from clinical review team are:

1. We refer to your amendment #55 (Part 2 complete snapshot analysis for

Study 111) submitted on April 15, 2011. There is a small difference in SVR rates that we are attempting to adjudicate. Please provide the USUBJID number for each subject you counted as achieving SVR, by treatment group.

2. We noted a patient who on study day 67 was hospitalized with epistaxis, purpura, and hepatorrhagia. Please provide a narrative for this subject (if one already exists, please inform us of its location within the NDA).

Thanks,
Pat

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MYUNG JOO P HONG
04/20/2011

Hong, Myung-Joo P.

From: Hong, Myung-Joo P.
Sent: Wednesday, April 20, 2011 4:33 PM
To: 'Chuck_Miller@vrtx.com'
Subject: RE: Telaprevir Clinical Request

Chuck, Russ requested to clarify the following:

- In your draft slide CS-25 you state that a total of (b) (4) telaprevir and (b) (4) Pbo subjects discontinued RBV due to anemia. In Table 47 it appears that (b) (4) telaprevir and (b) (4) Pbo subjects discontinued RBV primarily due to anemia.

thanks
Pat

From: Hong, Myung-Joo P.
Sent: Wednesday, April 20, 2011 4:17 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical Request

Thanks Chuck..... Very helpful.

Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, April 20, 2011 4:13 PM
To: Hong, Myung-Joo P.
Subject: Re: Telaprevir Clinical Request

Hi Pat,

these modification, interruptions, and discontinuations are predominantly due to anemia. We are also looking at the raw analyses generated for the Sulkowski EASL 2011 poster (IND 71,832, Seq 531) but those are T12 pooled from 108 and 111 vs Pbo (no C216).

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "'Chuck_Miller@vrtx.com'" <Chuck_Miller@vrtx.com>
Date: 04/20/2011 03:53 PM
Subject: Telaprevir Clinical Request

Chuck, Russ has this already. Please clarify if these are dose modifications, interruptions or discontinuations for ANEMIA only or ALL adverse events.

Thanks,
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, April 20, 2011 3:42 PM
To: Hong, Myung-Joo P.
Subject: Re: Telaprevir Clinical Request

Hi Pat,

Would Table 47 in Module 2.7.3 (Summary of Clinical Efficacy) suffice? I am including a screenshot of that here:



Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>

Date: 04/20/2011 02:26 PM
Subject: Telaprevir Clinical Request

Hi Chuck, request from clinical review team:

- Please provide the SVR rates for subjects who discontinued RBV due to anemia, who had a dose modification of RBV due to anemia, and those who had a dose interruption of RBV due to anemia.

Thanks,
Pat

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/s/

MYUNG JOO P HONG
04/20/2011

From: Hong, Myung-Joo P.
Sent: Tuesday, April 19, 2011 5:00 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical Request

Hi Chuck, additional requests from clinical review team are:

1. We refer to your amendment #55 (Part 2 complete snapshot analysis for Study 111) submitted on April 15, 2011. There is a small difference in SVR rates that we are attempting to adjudicate. Please provide the USUBJID number for each subject you counted as achieving SVR, by treatment group.
2. We noted a patient who on study day 67 was hospitalized with epistaxis, purpura, and hepatorrhagia. Please provide a narrative for this subject (if one already exists, please inform us of its location within the NDA).

Thanks,
Pat

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/s/

MYUNG JOO P HONG
04/19/2011



NDA 201917

INFORMATION REQUEST

Vertex Pharmaceuticals, Inc.
Attention: Antoinette Paone, MS, MBA
Director, Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) 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.

Concerning the Comparability Protocol for reworked (b) (4), the proposal as currently written is unacceptable. In particular, the submission category and the data needed to support a repeat of the (b) (4) require modification. The data supporting the acceptance of this protocol is represented by a single pilot-scale batch and will have a single commercial scale batch in support of the proposal upon fulfillment. This is not adequate. The Agency recommends the following changes to the protocol:

1. Submit release and 3-month stability data (long-term and accelerated) on at least three batches of reworked (b) (4) made at commercial scale. Include a comparison to routine (b) (4) lots, and an appropriate justification for the expiration dating period.
2. Submit release and 3-month stability data (long-term and accelerated) on at least one batch of telaprevir tablets made from 100% reworked (b) (4) and using commercial equipment. Include a comparison to routine tablet lots, and an appropriate justification for the expiration dating period.
3. The data listed in items 1 and 2 above should be reported by a CBE-30 supplement submitted prior to the release of any drug product containing reworked (b) (4) material.
4. Regarding validation of the rework process, we have the following additional comments: To demonstrate and ensure that the reworked material ((b) (4)) is acceptable for subsequent tablet manufacture, adequate process validation studies [e.g., process performance qualification (PPQ)] on a sufficient number of batches at a commercial scale will need to be conducted. Furthermore, for tablet lots manufactured from the reworked (b) (4) material, more extensive sampling than a typical routine production sampling plan is expected until sufficient knowledge (e.g., production and stability data) is generated to provide necessary statistical confidence of quality both within a batch and between batches. Adequacy of validation studies and results will be

evaluated on an inspection. Typically, coverage of process validation activities during a CGMP inspection includes review of study protocols, study execution and data, conclusions, and any changes made. Additionally, please note that concurrent release approaches are not acceptable in this type of instances. Refer to process validation guidance, section V, p16 for further information on this subject (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>).

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

Sincerely,

{See appended electronic signature page}

Stephen Miller, Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
04/19/2011

From: Hong, Myung-Joo P.
Sent: Tuesday, April 19, 2011 2:57 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir CMC Comment

Hi Chuck, as discussed at today's telecon please add the following statement to the label of the hospital unit dose bottle:

"Once opened use within 28 days. Keep bottle tightly closed."

Thanks,
Pat

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/s/

MYUNG JOO P HONG
04/19/2011



NDA 201917

GENERAL ADVICE

Vertex Pharmaceuticals, Inc.
Attention: Antoinette Paone, MS, MBA
Director, Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 29, 2011. The purpose of the meeting was to discuss responses to our information request letter dated March 16, 2011.

A copy of the official minutes of the meeting is attached for your information.

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

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, PhD
Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure – meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Tuesday, March 29, 2011
TIME: 15:30 – 16:30 ET
LOCATION: Teleconference
APPLICATION: NDA 201917
DRUG NAME: telaprevir tablets

FDA ATTENDEES: (Title and Office/Division)

Sharmista Chatterjee, PhD, CMC Lead for QbD
Bogdan Kurtyka PhD, Product Quality Reviewer
Christine Moore, PhD, Deputy Director, Science and Policy
Meiyu Shen, PhD, Mathematical Statistician
Stephen Miller, PhD, Branch Chief
Lin Qi, PhD, Product Quality Reviewer
Patrick Marroum, PhD, Biopharmaceutics Supervisor
Christopher Hough, PhD, Product Quality Reviewer
Sandra Suarez-Sharp, PhD, ONDQA/Biopharmaceutics Reviewer
Don Henry, Regulatory Project Manager
Tara Goen, Team Leader, Office of Compliance
Terrance Ocheltree, PhD, Director, ONDQA Division II
Yi Tsong, PhD, Deputy Director, Biometrics

VERTEX ATTENDEES:

Antoinette Paone, M.S., MBA, Director, Regulatory Affairs-CMC
Patricia Hurter, Ph.D., Vice President, Pharmaceutical Development
Thomas Gandek, Ph.D., Sr. Director, Technical Operations
John Weet, Ph.D., Vice President, Regulatory Affairs
Prabu Nambiar, Ph.D., MBA, RAC, Vice President, Regulatory Affairs-CMC
Carole Varanelli, M.S., Vice President, Quality
Geny Doss, Director, GMP Quality
Stephanie Krogmeier, Ph.D., Manager, Regulatory Affairs-CMC
Craig Dunbar, Ph.D., Sr. Director, Formulation Development
Jeffrey Katstra, M.S., Sr Scientist, Formulation Development
Eda Ross Montgomery, Ph.D., Sr. Director, Quality, CMC and QbD
(b) (6) Statistician, Independent Consultant
David Nadig, Ph.D., Sr. Director, Analytical Development
Kelly Tolton, Ph.D., Associate Director, Technical Operations

BACKGROUND:

The Agency issued an information request letter dated March 16, 2011, which identified several comments and recommendations that needed to be addressed in order to continue the review of the application. Upon receipt and review of the letter, Vertex requested a teleconference to gain clarity on two items contained in the letter:

1. Based on our evaluation, we do not agree with your conclusion that (b) (4). It is recommended that tablet weight gain be identified as a Key IPC and included in Section 3.2.P.3.3 and 3.2.P.3.4 to ensure consistent control between commercial and clinical products.
2. Your proposed dissolution specification is not acceptable as it does not provide satisfactory assurance of bioequivalence to the bio-batches. We recommend the following alternatives:
 - a. Option I - Revise your dissolution specification as: Q= (b) (4) in 20 minutes

This recommendation is based on data from the clinical/bioequivalence and stability batches and we consider that it is more sensitive to product variations than your proposed specification of Q= (b) (4).

(b) (4)

- b. Option II - Alternatively, we will also consider a model predicted dissolution specification of Q= (b) (4) as a surrogate for in lab dissolution testing. To support this approach, provide data showing validation of the dissolution model, including external/independent data to verify model predictions. Submit the validation data (as SAS Transport files) and report. Additionally, comment on the approaches that will be used to maintain and update the model.

For item #2, Vertex requested further discussion regarding Option II, only.

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/s/

TERRANCE W OCHELTRIE
04/15/2011

From: Hong, Myung-Joo P.
Sent: Friday, April 15, 2011 4:12 PM
To: 'Chuck_Miller@vrtx.com'
Subject: telaprevir Responses to Requests

Hi Chuck, the responses I received from our review team are listed below.

Also, for your AC slides, would you clarify the following things:

Slide 26: Telaprevir is an inhibitor of CYP3A **and P-gp**

Slide 27: "Minimal impact of renal impairment on **single-dose** telaprevir PK"

thanks,
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Friday, April 15, 2011 1:02 PM
To: Hong, Myung-Joo P.
Subject: NDA 201,917 Clinical Pharmacology Requests

Hi Pat,

our clinical pharmacology group has been working through two comments/requests that were discussed during our call with DAVP on 24 March 2011 (the meeting to finalize the Vertex backgrounder). During the call, the FDA Clinical Pharmacologist noted that we should provide the methadone protein binding displacement and also noted the assessment of the renal impairment study. Our clinical pharmacologist indicated that we would provide information back relating to both. We now have the following responses prepared:

1. Summary of methadone protein binding displacement (data from subjects in Study C135).
2. Renal impairment: Simulation of multiple doses.

Would it be acceptable to submit them at this time?

FDA Response: Please do not submit modeling and stimulation at this point. We won't be able to review it before the PDUFA goal date. We may ask at a later time as PMR/PMC, still pending discussion. Clinical Pharmacology group may have found the methadone binding study Vertex is referring to. Please confirm if it is a study report FK7501. If so, there is no need to re-submit.

Also, we note a minor error in the FDA's briefing document (Page 3, under Hepatic impairment):

For Child Pugh Class B, telaprevir exposures were reduced by 46% (not (b) (4) as mentioned): Please see Table 11- 2 (page 56 of Study Report VX06-950-012) - the ratio of log-transformed AUC_{0-8h} is 54%. The text (page 48 and the synopsis of the study report) has a typo (b) (4). It may not make a difference for the upcoming meeting, but we would like to make sure you are aware of the difference between Vertex's briefing document and FDA's document.

FDA Response: Russ found that (b) (4) of telaprevir subjects had a hemoglobin level <10 g/dL and Vertex says it was (b) (4). Similarly, for <8.5

I found 247 (14%) and they found (b) (4). Could you provide the data supporting their numbers.

Take care and best regards,

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

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/s/

MYUNG JOO P HONG
04/15/2011

From: Hong, Myung-Joo P.
Sent: Thursday, April 14, 2011 5:13 PM
To: 'Chuck_Miller@vrtx.com'
Subject: RE: NDA 201,917 - (b) (4) Questions for the Division

Hi Chuck, our responses are addressed in blue font below. I wanted to remind you that Russ Fleischer will not be able to review anything (including protocol concepts) until after AC meeting.

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Thursday, April 14, 2011 10:05 AM
To: Hong, Myung-Joo P.
Subject: NDA 201,917 - (b) (4) Questions for the Division

Good morning Pat,

(b) (4)

I did have a few questions for you and the review team:

1) Would it be acceptable to send the FDA's ACM Briefing Document to other Health Authorities (e.g., France, Sweden, Switzerland, Canada, etc) that request it in advance of the meeting on the 28th?

FDA Response: We will send FDA AC backgrounder to Canada and Sweden Health Authorities thru Office of International Program.

2) Vertex submitted four protocol concepts in Sequence 0530 of IND 71,832 in anticipation of PMC discussions with the Division per the Day 60 Letter. Comments on the concepts would be greatly welcomed by Vertex as we are prepared to rapidly finalize protocols if Telaprevir is approved. Do you anticipate that you will have comments on the concepts around the time of the PMC discussion (2 May 2011) indicated in the Letter?

FDA Response: We will not be able to discuss PMR/PMCs until after we hear the advice of the AC. Our clinical reviewer may or may not have time to look at the concepts in the next couple of weeks.

3) A country specific substudy of Study C219 (the rollover study from the placebo arm of Study C216) enrolled a small number of subjects who failed a short duration of telaprevir therapy from Studies 101 and 103. These subjects are currently being retreated with T/PR. This is the first data showing retreatment with

TVR in subjects who failed TVR in a prior study. We have received an interim analysis of on-treatment data. It is very early data in a small number of subjects. Would the Division like this interim analysis submitted to IND 71,832?

FDA Response: Interim study results can be submitted to the IND but it's not likely that these will be reviewed prior to the AC nor should they be introduced by Vertex at the AC without division review.

Best regards,

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

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/s/

MYUNG JOO P HONG
04/14/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, April 13, 2011 2:23 PM
To: 'Chuck_Miller@vrtx.com'
Cc: Fava, Walter; Mena-Grillasca, Carlos
Subject: Telaprevir Packaging Configuration

Hi Chuck, we acknowledge the receipt of your April 6, 2011 submission which contains a summary report as requested in my previous e-mail.

The summary report does not include details of the methodology and also states that the "objectives of the study were to asses individual package options with focus on compliance, portability, privacy, package size, and ease of opening providing a comparison of package alternatives, and to make recommendations for improvement."

DMEPA would need more information about how the blinded one on one interviews were conducted including what instructions were given to participants, what questions were asked, what prompts were given, along with the responses. Information concerning the design of the study is lacking for us to determine how the company made the conclusions in the summary report. Qualitative and quantitative data would also be useful which shows for example, since 26 patients and 11 healthcare practitioners were interviewed, what were the actual responses from each participant throughout all phases of the interview/study process and the resultant percentages for each outcome measurement. Participant demographics along with inclusion and exclusion criteria is also useful for our assessment.

Would you submit your response by April 19, 2011?

Thanks,
Pat

From: Hong, Myung-Joo P.
Sent: Thursday, March 31, 2011 10:15 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Packaging Configuration

Hi Chuck, DMEPA division is fine to receive the information by next Wednesday. In addition to the summary report, would you submit the raw data along with previous prototypes and revisions Vertex made as a result of the testing Vertex performed?

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, March 30, 2011 5:21 PM
To: Hong, Myung-Joo P.
Subject: Re: Telaprevir Packaging Configuration

Hi Pat

I just got off the phone with our Trade and Distribution people. We do in fact have a lot of information (comprehension studies, focus groups, and so on) regarding how we arrived at the packaging configuration and graphics related to dosing. We will create a summary of the research and provide the source information in an Appendix. The research spans about 3 or 4 years and covers numerous different types of prototypes that were dismissed in favor of the currently proposed packaging. . We can submit this all to you by next Wednesday. Will that work for you?

Best regards

Chuck

From: "Hong, Myung-Joo P." [Myung-Joo.Hong@fda.hhs.gov]
Sent: 03/30/2011 12:13 PM AST
To: Chuck Miller
Subject: Telaprevir Packaging Configuration

Hi Chuck, has Vertex done any comprehension studies or usability studies for the proposed packaging configuration of telaprevir? DMEPA is concerned about dosing errors that may result from two tablets being packaged in the same blister, and whether patients will understand the graphics on the carton labeling showing them how to take two tablets with food three times a day. If Vertex has any data to support the use of the graphics or the packaging configuration, it would be helpful for us to make our recommendations.

Thanks,
Pat

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/s/

MYUNG JOO P HONG
04/13/2011

From: Hong, Myung-Joo P.
Sent: Monday, April 11, 2011 1:34 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical Request

Hi Chuck, would you provide the number of women in the Phase 3 trials who were on hormone-based contraceptives (by treatment group: telaprevir and Pbo)?

Thanks,
Pat

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/s/

MYUNG JOO P HONG
04/11/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, April 06, 2011 1:35 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical Requests

Hi Chuck, additional requests from clinical review team:

1. Please identify subjects who had thrombocytopenia. For these subjects, please provide whether any had a bleeding event related to low platelet count, or did any receive a platelet transfusion.

2. Please identify subjects who had neutropenia. For these subjects, please provide whether there were any events of febrile neutropenia, severe infection related to low neutrophil counts, or if any subjects received a CSF product.

If there were subjects who received either a platelet transfusion or treatment with a CSF product, please provide a narrative.

Thanks
Pat

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/s/

MYUNG JOO P HONG
04/06/2011

Henry, Don

From: Henry, Don
Sent: Friday, April 08, 2011 4:04 PM
To: 'Antoinette_Paone@vrtx.com'
Subject: NDA 201917 information request

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) 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.

We want to acknowledge the information you provided prior to the teleconference on the film-coating process, and the discussion during that meeting. (b) (4)

[REDACTED] (b) (4)

Therefore, we recommend the film-coating (b) (4).
We feel that additional supporting information is needed if the upper limit of (b) (4) is important from the manufacturing perspective. This justification would need to address the revised dissolution acceptance criteria.

If you have any questions, feel free to contact me

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
04/08/2011



**MEMORANDUM OF MEETING MINUTES
(INTERNAL)**

MEETING DATE: March 16, 2011
TIME: 2 - 3:30 pm
LOCATION: White Oak Conference Room 6396
APPLICATION: NDA 201-917
DRUG NAME: Telaprevir
TYPE OF MEETING: Informal Advice for Advisory Committee Meeting

FDA ATTENDEES:

Debra Birnkrant, M.D., Division Director
Jeff Murray, M.D., Deputy Division Director
Linda Lewis, M.D., Clinical Team Leader
Russ Fleischer, PA-C, MPH, Clinical Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology TL
Shirley Seo, Ph.D., Clinical Pharmacology Reviewer
Shashi Amur, Ph.D., Clinical Pharmacology Reviewer
Jiang Liu, Ph.D., Clinical Pharmacology Reviewer
Pravin Jadhav, Ph.D., Clinical Pharmacology Reviewer
Hanan Ghantous, Ph.D., Pharmacology/Toxicology Team Leader
Mark Powley, Ph.D., Pharmacology/Toxicology Reviewer
Tom Hammerstrom, Ph.D., Statistical Reviewer
Greg Soon, Ph.D., Statistical Team Leader
Lisa Naeger, Ph.D., Clinical Virology Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Patrick Harrington, Ph.D., Clinical Virology Reviewer
Kendall Marcus, M.D., Safety Deputy Director
Vicky Tyson, Chief Project Manager
Patricia Hong, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Vertex Pharmaceutical, Inc.

Chuck Miller, Director, Regulatory Affairs
Varun Garg, Ph.D., Senior Director, Clinical Pharmacology
Josh Henshaw, Ph.D., Senior Pharmacometrician, Clinical Pharmacology
Darryl Patrick, DVM, Ph.D., Vice President, Exploratory Development
Graeme Smith, Ph.D. DABT, Director, Toxicology
John F. Weet, Ph.D. Vice President, Regulatory Affairs
Robert Kauffman, M.D., Ph.D., Sr. Vice President, Clinical Development & CMO

Tara L. Kieffer, Ph.D., Associate Director, Clinical Virology
Antonia Kolokathis, M.D., Senior Vice President, Global Medical Affairs & Patient Safety
Abdul Sankoh, Ph.D., Senior Director, Biometrics
Ann Kwong, Ph.D., Vice President, HCV Franchise Lead
Shelley George, M.D., Vice President, HCV Therapeutic Area Lead
Elena Koudourakis, Ph.D., Vice President, Global Registration Leader
Nathalie Adda, M.D., Senior Medical Director, Clinical Development
Priya Singhal, M.D., MPH, Senior Medical Director, Global Patient Safety (via telephone)

External:

Dominik Naessens, PhD (Pharm), M.B.A. Associate Director, EMEA Regulatory Liaison Global Regulatory Affairs Johnson & Johnson Pharma, Tibotec BVBA (via telephone)

(b) (4)

BACKGROUND:

The teleconference was held to discuss preliminary issues in regards to the advisory committee (AC) meeting scheduled for April 28, 2011 and AC meeting background materials. The Division of Antiviral Products (DAVP) provided some general guidelines about the AC meeting and the backgrounder.

DISCUSSION:

DAVP commented that the AC background materials were just received on March 14, 2011, and DAVP hasn't completed the review but asked Vertex about the outline for their presentation at the AC meeting. Vertex plans to allocate the 1.5 hours as follows:

Introduction:	5 minutes
Clinical Development:	10 minutes
Efficacy Study:	30 minutes
Safety Study:	30 minutes
Benefit/Risk:	10 minutes

DAVP recommended Vertex keep the background materials short and avoid redundancy of the presentation materials. After Vertex's presentation, the FDA presentation will follow, by Russell Fleischer, for a total of 45 minutes to one hour.

DAVP commented the Federal Notice was released and the AC meeting background material can be discussed by April 1, 2011. DAVP asked Vertex to delete any comments about labeling and for the safety database to focus on the Phase 3 data only or include an Appendix. DAVP plans to have more follow-up discussions/comments with Vertex in regards to specific/different issues arising during review cycle.

DAVP will have additional comments on the slides and will finalize specific questions before the AC meeting.

DAVP opened the discussion to the other discipline's reviewers but no one had any comments.

DAVP recommended Vertex remove the proprietary name from the background materials until a new name is accepted. Vertex will replace (b) (4) with "telaprevir" in the background materials.

Vertex asked a question related to SVR and stated they are discussing how to handle differences. DAVP responded we are still reviewing the data and discussing this issue and will get back with Vertex to come to an agreement on SVR before the background material is submitted to the AC committee. DAVP plans to talk to Vertex again in few days.

There was discussion about participation of consultants at the AC meeting. DAVP stated that a dermatologist is on the review panel and we will let them know when they are cleared. Also, our cardiology Division was consulted, the QT study is complete and since there was no significant QT or PR prolongation effects with telaprevir in TQT study the cardiologists do not need to be present at AC meeting.

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/s/

MYUNG JOO P HONG
04/04/2011

From: Hong, Myung-Joo P.
Sent: Thursday, March 31, 2011 1:43 PM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201,917 IRT Review Memo

Attachments: ViewDocument.pdf

Hi Chuck, we had more discussion among review team and decided that we can send "Section 1" of IRT's review memo. It is attached here.

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Monday, March 28, 2011 1:43 PM
To: Hong, Myung-Joo P.
Subject: NDA 201,917: Update and Requests on behalf of the team

Good afternoon Pat,

I wanted to provide you with an update regarding the ACM Background Document. After working on the document following our call last Thursday, we have trimmed it down by a number of pages based on the feedback provided. We should have addressed all of the major concerns that were raised and it is a better document as a result. Once again, thank you. It was sent to Paul on Friday and should be at his desk any time now.

Also, with regards to the report that the CDER IRT has created for Study C136, I was wondering if it would be possible to see a copy? I noticed in the MAPP for IRT (bottom of page 3) that the RPM is supposed to provide the comments to the review team prior to sending to the Sponsor (see link below). When I read this, it seemed that we could receive a copy of the report. If this is possible, I would greatly appreciate it.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082015.pdf>

The other question I have relates to the Division's assessment of SVR. Would it be possible to see your conclusion (i.e., SVR rates)? Russ has indicated a few times that they are likely to be higher, so I am trying to manage expectations here a little.

Take care and best regards... I hope Spring has materialized in DC... we are experiencing a slightly bitter cold up here in New England... hard to believe April is a couple days away!

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

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/s/

MYUNG JOO P HONG
03/31/2011



NDA 201917

GENERAL ADVICE

Vertex Pharmaceuticals, Inc.
Attention: Antoinette Paone, MS, MBA
Director, Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 3, 2011. The purpose of the meeting was to gain clarification on the information provided to support the statistical evaluation of the model for the (b)(4).

A copy of the official minutes of the meeting is attached for your information.

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

Sincerely,

{See appended electronic signature page}

Stephen Miller, PhD
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure – meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Thursday, March 3, 2011
TIME: 11:30 – 12:30 ET
LOCATION: FDA White Oak Facility, Building 21, Room 1309
APPLICATION: NDA 201917
DRUG NAME: telaprevir tablets

FDA ATTENDEES: (Title and Office/Division)

Sharmista Chatterjee, PhD, CMC Lead for QbD
Bogdan Kurtyka PhD, Product Quality Reviewer
Christine Moore, PhD, Deputy Director, Science and Policy
Meiyu Shen, PhD, Mathematical Statistician
Stephen Miller, PhD, Branch Chief
Lin Qi, PhD, Product Quality Reviewer
Patrick Marroum, PhD, Biopharmaceutics Supervisor
Christopher Hough, PhD, Product Quality Reviewer
Sandra Suarez, PhD, ONDQA/Biopharmaceutics Reviewer
Don Henry, Regulatory Project Manager
Vibhakar J. Shah, Senior Policy Advisor (via phone)
George Lunn, PhD, Product Quality Reviewer (via phone)

VERTEX ATTENDEES:

Antoinette Paone, M.S., MBA, Director, Regulatory Affairs-CMC
Patricia Hurter, Ph.D., Vice President, Pharmaceutical Development
Thomas Gandek, Ph.D., Sr. Director, Technical Operations

Via phone:

John Weet, Ph.D., Vice President, Regulatory Affairs
Prabu Nambiar, Ph.D., MBA, RAC, Vice President, Regulatory Affairs-CMC
Carole Varanelli, M.S., Vice President, Quality
Geny Doss, Director, GMP Quality
Stephanie Krogmeier, Ph.D., Manager, Regulatory Affairs-CMC
Craig Dunbar, Ph.D., Sr. Director, Formulation Development
Jeffrey Katstra, M.S., Sr Scientist, Formulation Development
Eda Ross Montgomery, Ph.D., Sr. Director, Quality, CMC and QbD
(b) (6) Statistician, Independent Consultant
David Nadig, Ph.D., Sr. Director, Analytical Development
Kelly Tolton, Ph.D., Associate Director, Technical Operations

BACKGROUND:

As part of the information request letter dated September 28, 2010, the Agency requested information regarding the qualification of the proposed dissolution model. After completing the model qualification protocol, Vertex requested a meeting to discuss the outcome and path forward. The Agency agreed to the meeting, and also requested discussion regarding the effects of the particle size acceptance criteria in the specification for the (b) (4). The following comments were provided to Vertex prior to the meeting:

1.

(b) (4)

2.

(b) (4)

(b) (4)

3. In view of the recent results of qualification of dissolution model, and our evaluation of the model that shows that the model does not account for variability between experiments (b) (4) we would like to get an understanding of Vertex's thinking about the applicability of the dissolution model.

DISCUSSION POINTS AND ACTION ITEMS:

During the meeting, Vertex presented the following proposal to address recent discussion topics:

1. Remove (b) (4). Vertex will continue to use the PAT based on line method for testing particle size for in process monitoring.
2. Withdraw (b) (4)
3. Remove the (b) (4) from the specification for (b) (4) particle size/bulk density and hardness models. However, keep (b) (4) as defined for the low risk model, i.e. (b) (4) for particle size and bulk density.

Regarding Vertex's proposal to submit trending data for all registered models in an annual report, the agency commented that in accordance with ICH Q8(R2) all movements within the design space are managed by the firms own quality system which includes trending data of supporting models. Thereby, Vertex is not required to submit the trending data in an annual report, however, they may submit if they choose to do so.

Regarding the qualification of the dissolution model, Vertex indicated that the qualification did not meet the protocol acceptance criteria. (b) (4) However, based on the results obtained from the qualification, the failure to qualify the model is not expected to adversely impact the specification for (b) (4) particle size and bulk density or the proposed design space. Vertex requested input regarding the impact of failure of model qualification on the release of future commercial manufacturing lots from a GMP perspective.

Post meeting discussion:

1. Your rationale for failing the pre-determined protocol acceptance criteria for the dissolution model seems reasonable. However, it is our expectation that efforts will be continued to qualify the model as more manufacturing experience is gained and relevant data representative of the process are acquired.

From a risk perspective and given the current control strategy (i.e. testing hardness and dissolution of tablets), your assessment that failure to qualify the model is not expected to adversely impact the product quality of future commercial lots, seems plausible. Nevertheless, the responsibility to evaluate all factors impacting the product quality and to determine accept/reject decision for the batch release rests not only with the quality unit of your contract manufacturing site but also ultimately with quality unit under your quality system.

Any deviations from the established NORs and PARs for the process parameters as well as material attributes are expected to be thoroughly investigated, and followed-up in a timely manner for corrective and preventive actions as appropriate and per the established procedures. Appropriate documentation of deviations and follow-up actions is expected and subject to audit on inspection.

2. With regards to the model, we can summarize our comments on the sponsor's proposal in two points. First, the modeling interest is to evaluate the response of the model not the slope or intercept. Second, with a (b) (4), the interest is the model response not the mean response.

As the review team continues the evaluation, an information request may be generated to clarify the above points and other issues

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/s/

STEPHEN P MILLER
03/28/2011

From: Hong, Myung-Joo P.
Sent: Thursday, March 24, 2011 10:47 AM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201,917 - Questions for consideration in advance of the Thursday teleconference

Hi Chuck, our preliminary responses are added below.

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, March 23, 2011 11:42 PM
To: Hong, Myung-Joo P.
Subject: NDA 201,917 - Questions for consideration in advance of the Thursday teleconference

Good evening Pat,

in advance of our teleconference scheduled from 2pm-3pm on Thursday, we had 3 questions related to topics that impact the background document. If possible, we would like to address these questions, in addition to the primary endpoint discussion.

1. At this time, the Vertex ACM background document contains a section describing RGT for prior relapsers but the presentation does not discuss this proposal. Does the Division have additional feedback regarding the proposal for response guided therapy for prior relapsers as it pertains to the background document or presentation?

FDA Response: We will be providing some additional analyses evaluating the RGT for prior relapsers. It may be appropriate for you to present your rationale for your RGT recommendation in this subgroup, as this treatment approach was not formally studied in the pivotal studies.

2. During the review phase, the Division has requested additional data (e.g. Viral dynamic modeling) to support the stopping rules proposed in NDA 210,917. Does the Division recommend that Vertex include a discussion of these stopping rules in the presentation or only as backup in response to questions from the committee?

FDA Response: We do not believe the proposed stopping rules need to be discussed during the Advisory Committee meeting. This issue will likely be part of our labeling discussions later in the review cycle. Backup slides could be used in the event the committee has questions.

3. The background document contains a data cut from Study 110 (HIV/HCV coinfection) that is not included in the original NDA but has been presented publicly at CROI 2011 in February. Is this acceptable to the Division?

FDA Response: The data from Study 110 presented at CROI was extremely preliminary and, if presented, should be presented as such. At the time of the CROI presentation, the study was not fully enrolled and only limited data through 12 weeks were available. It is likely that the committee will be interested in how the study is progressing and what additional plans are being made to evaluate the HIV/HCV co-infected population.

One additional question we have relates to the draft USPI and an omission of data from the T8 arm in the recently updated AE section.

4. The updated draft USPI that was recently submitted to the Division contained an AE analysis that included the phase 3 controlled and uncontrolled studies but the T8 arm was omitted. Based on the recent teleconference we became aware that the Division is including the T8 arm in the pooling. Should Vertex resubmit the draft USPI with the updated AE tables including the T8 arm?

FDA Response: It is our intention to include the T8 arm in the AE table but it may be preferable for you to wait until we send a more complete draft label and make updates at that time.

Best regards,

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

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/s/

MYUNG JOO P HONG
03/24/2011

From: Hong, Myung-Joo P.
Sent: Monday, March 21, 2011 11:18 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir.CP comment related to PKPD dataset

Hi Chuck, question from clinical pharmacology review team in regards to PKPD.xpt dataset :

In the previous PKPD.xpt dataset (Seq 0024), the patient's prior treatment status (PRIORTRT) in Study 106 was classified as **NON RESPONDER**, **RELAPSER**, and **VIRAL BREAKTHROUGH**. However, in the revised dataset (Seq 0044), PRIORTRT was classified as **NULL RESPONDER**, **RELAPSER**, and **VIRAL BREAKTHROUGH**. Is the **NULL RESPONDER** following the definition in the FDA guidance? If they are actual **NON RESPONDERS**, can you classify them into **PARTIAL RESPONDER** and **NULL RESPONDER** by following the definition in the FDA guidance?

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Thursday, March 17, 2011 3:44 PM
To: Hong, Myung-Joo P.
Subject: NDA 201,917 - PKPD.XPT Dataset Submitted in Seq 0024

Hi Pat,

as we discussed, I am attaching a Word Document that contains the summary of our investigation into the errors that were found in the PKPD.XPT dataset that we submitted in Seq 0024 to NDA 201,917. As I stated on the phone, this dataset was created by a team that did not have responsibilities for creation of other custom datasets submitted during the review phase and the errors contained in the dataset do not reflect the quality or integrity of the other datasets we have provided during the review phase.

We hope that this does not cause any problems for the reviewer who requested the dataset. In the process of investigating the errors, a new dataset was created by an independent team using the standards and procedures that should have been followed originally. Also, as stated, the supervisor who led the original team for PKPD.XPT is no longer with Vertex.

In the event that a replacement dataset is needed, we have one ready for submission. In addition, should the reviewer need to rerun any analyses, we would like to extend any assistance that they may need (e.g., direct phone connection to SAS programming team to run analyses, clinical pharmacometrician support).

Please let me know if you need any additional details. We are very cognizant of the review timeline and would like to avoid any delays by providing any additional assistance or support that is necessary.

Best regards,

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

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/s/

MYUNG JOO P HONG
03/21/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 18, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: March 18, 2011

NDA: 201-917/Original Submission

TO: John Weet, Ph.D.

FROM: Myung-Joo Patricia Hong, Regulatory Project Manager

SPONSOR: Vertex Pharmaceuticals, Inc.

SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Clinical

1. Please populate the following table for the following laboratory abnormalities that occurred during the T/Pbo dosing period. For each parameter, please include the value used to determine \geq Grade 3 toxicity and the source for that value. For any parameter for which data is missing, please provide an explanation.

N (%)	T/PR N=1797	Pbo/PR48 N=493
ALT All Grades \geq Grade 3		
AST All Grades \geq Grade 3		
Total Bilirubin All Grades \geq Grade 3		
\uparrow Glucose All Grades \geq Grade 3		
Total Cholesterol All Grades \geq Grade 3		

Triglycerides All Grades ≥Grade 3		
↑Thyroid stimulating hormone All Grades ≥Grade 3		
↓Thyroid stimulating hormone All Grades ≥Grade 3		
↑ Amylase All Grades ≥Grade 3		
↑ Lipase All Grades ≥Grade 3		

2. Please confirm if cholesterol, triglyceride and glucose levels were obtained in the non-fasting or fasting state.

Please provide your response by March 22, 2011.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

MYUNG JOO P HONG
03/18/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 17, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: March 17, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Pharmacology/Toxicology

1. We have reviewed your March 9, 2011 submission which was submitted in response to our March 2, 2011 request to provide systemic exposure values normalized over 24 hr. Using the same approach, please provide Day 182 AUC_{0-24 hr} values for all doses evaluated in the 6-month rat study (VX-950-TX-020).
2. In response to your additional request, we are providing rationale for modifying the fertility information in the label.

Effects on fertility parameters were noted in Study no. VX-950-TX-019. While it appears as though the fertility index (i.e., # of pregnancies/# of rats that mated) was not affected by telaprevir treatment, changes in several other important parameters were noted. Effects listed in the proposed label were observed following cohabitation of treated males + treated females and treated males + untreated females. In addition to the histopathological analysis and sperm evaluation, the data supports fertility effects in male rat. Because the study did not include an untreated male + treated female group, conclusions cannot be made in regards to female effects.

It is also not clear that the testicular effects can be classified as species-specific. While degenerative testicular lesions were not observed in the dog, we are not aware of an evaluation that could be used to rule out a potential clinical correlate. In addition to the suggested labeling change previously provided, we suggest adding the following sentence to the proposed labeling:

Degenerative testicular toxicity was not observed in chronic toxicity studies in the dog.

Impairment of Fertility

Telaprevir treatment had effects on fertility parameters in rats. The no observed adverse effect level (NOAEL) for testicular toxicity was established at exposures 0.17-fold the human exposures at the recommended clinical dose. Potential effects on sperm (e.g., decreased percentage motile sperm and increased non-motile sperm count) were observed in a rat fertility study at exposures 0.30-fold of human exposures at the recommended clinical dose. Additional effects on fertility include minor increases in the percentage of dams with nonviable embryos and percentage of nonviable conceptuses per litter. These effects are likely associated with testicular toxicity in male but contributions of the female cannot be ruled out. Degenerative testicular toxicity was not observed in chronic toxicity studies in the dog.

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Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

MYUNG JOO P HONG
03/17/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, March 16, 2011 11:55 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir FDA Response and Additional Comment

Hi Chuck, please see our response below for your question. We have an additional comment:

"Please provide the number of subjects who relapsed at each FU visit (number at FU-4, number at FU-12 and number at FU-24) for each treatment group."

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Thursday, March 03, 2011 4:33 PM
To: Hong, Myung-Joo P.
Subject: Re: NDA 201-917 Labeling comments

Hi Pat,

with respect to Item #4 in the Comments PDF, we have a request for clarification. The Division's comments are in bold italics and Vertex's response is in normal text.

FDA Comment

Statistical

4. Please compute table of SVR24 using the snapshot at week 24 post EOT with missing replaced by LOCF and using an LOQ of 25.

Vertex Response

In the snapshot analysis, the virologic outcome will be based on the HCV RNA assessment in a visit window defined as below:

For subjects assigned total treatment duration of 24 weeks, the visit window will be week 32-78.
For subjects assigned total treatment duration of 48 weeks, the visit window will be week 56-78.

In addition, LOQ of 25 will be used to determine the virologic response in the follow-up period in the visit window.

Treatment Success will be defined as subjects who have HCV RNA <25 IU/mL in the defined visit window.

Does the Division agree? FDA: Yes, we agree.

Would the Division like to have the revised SVR tables incorporated into the draft labelling to be sent back to the Division by the 9th of March?

Best regards,

Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 03/02/2011 12:13 PM
Subject: NDA 201-917 Labeling comments

Hi Chuck, attached is our labeling comments and proposal. The word file is also attached for your follow up work. Please respond by March 9, 2011.

Do you have conference call # for our March 16 meeting?

thanks [attachment "ViewDocument.pdf" deleted by Chuck Miller/BOS1/VRTX]
[attachment "3.2.11.Telaprevir PI to Vertex.doc" deleted by Chuck Miller/BOS1/VRTX]

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/s/

MYUNG JOO P HONG
03/16/2011



NDA 201917

INFORMATION REQUEST

Vertex Pharmaceuticals, Inc.
Attention: Antoinette Paone, MS, MBA
Director, Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) 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.

Drug Substance:

1. We have the following recommendations for the Sunset Provision for (b)(4) Testing. We are also willing to consider alternative approaches to achieve comparable risk-control.

In general, we agree with your approach to exclude (b)(4) testing from the drug substance specification through a CBE-30 supplement, but with limiting conditions. We do not find data to assure removal of (b)(4) throughout the proposed PARs. Therefore, modify the ranges in your proposal to the NORs (b)(4), or provide data to ensure removal of (b)(4) throughout the PARs, or minimally at highest risk conditions (b)(4).

Additionally, include in your proposal a commitment to perform testing on a risk-driven basis if changes are made or deviations occur to the process that could result in increased levels of (b)(4) in the drug substance. In addition, please also include a commitment to periodically test for (b)(4), at minimum on an annual basis.

We are currently exploring within CDER how to document testing that is performed on a periodic and/or risk-driven basis. We recommend that you arrange a teleconference with us prior to the submission of the CBE-30 supplement to discuss current preferred approaches.

- (b) (4)
2. Following the teleconference held on March 3, 2011, we understand that the proposed Real Time Release for (b) (4) particle size will be removed from (b) (4) specification. As a consequence, the request included in the IR letter dated November 8, 2010, where you were asked to indicate in the specification sheet what the primary analytical method for particle size measurement was, is no longer relevant.
 3. Correct acceptance limits in the specification and master batch record for particle size d_{50} to read:

(b) (4)

4. Confirm that BD in the formula (b) (4)
5. We consider an expiration dating period of (b) (4) to be appropriate for the (b) (4), and understand your use of the term “shelf life” in Section 3.2.P.8.1 to be consistent with this approach. However the Certificate of Analysis for (b) (4) attached to the executed batch record for batch 17QB01.HQ00071 lists a “retest date”. Clarify that you do not intend to retest the (b) (4) to extend the expiration dating.

Telaprevir tablet:

6. Revise the specifications for maximum allowable (b) (4) (b) (4) to confirm with information provided in your submission. It is indicated in Table 8 in 3.2.P.2.3 that maximum allowable (b) (4) (b) (4).
In addition, you have indicated that USP specifications would be adopted for the excipients. However, the USP limits for (b) (4) are higher than the limits specified in your submission (b) (4) (b) (4).
7. Regarding the analytical procedure for physical-form-tablet by (b) (4) (b) (4)
 - a. (b) (4) (b) (4)
 - b. (b) (4)

8. Based on our evaluation, we do not agree with your conclusion that (b) (4).
(b) (4). It is recommended that (b) (4) and included in Section 3.2.P.3.3 and 3.2.P.3.4 to ensure consistent control between commercial and clinical products.
9. In general, NOR is always less than or equal to PAR (b) (4).
(b) (4) Clarify.
10. Modify the acceptance criteria for individual unspecified impurity to (b) (4) for drug product, since the identification threshold is 0.10% for maximum daily dose > 2 g/day according to ICH Q3B(R).
11. Clarify whether the post-approval stability studies will include tablet lots which are manufactured using (b) (4) from each (b) (4) supplier.
12. Your proposed dissolution specification is not acceptable as it does not provide satisfactory assurance of bioequivalence to the bio-batches. We recommend the following alternatives:
- a. Option I - Revise your dissolution specification as: $Q = (b) (4)$ in 20 minutes
- This recommendation is based on data from the clinical/bioequivalence and stability batches and we consider that it is more sensitive to product variations than your proposed specification of $Q = (b) (4)$.
- To facilitate your implementation of this approach, the agency would accept the following dissolution specification and time point as the trigger limit for (b) (4):
(b) (4)
(b) (4)
- b. Option II - Alternatively, we will also consider a model predicted dissolution specification of $Q = (b) (4)$ at 15 minutes as a surrogate for in lab dissolution testing. To support this approach, provide data showing validation of the dissolution model, including external/independent data to verify model predictions. Submit the validation data (as SAS Transport files) and report. Additionally, comment on the approaches that will be used to maintain and update the model.

Comparability protocol:

13. Your proposed design space comparability protocol is not acceptable. Our concerns include but are not limited to:

a.

b.

(b) (4)

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

Sincerely,

{See appended electronic signature page}

Stephen Miller, Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
03/16/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 14, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: March 14, 2011
NDA: 201-917/Original Submission
TO: John Weet, Ph.D.
FROM: Myung-Joo Patricia Hong, Regulatory Project Manager
SPONSOR: Vertex Pharmaceuticals, Inc.
SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comment from the review team:

Clinical Pharmacology

We note that pyrazinoic acid (PZA) is a major metabolite of pyrazinamide and a structural analog of niacin, which have been associated with pruritis, flushing, and rash. In your exploratory analysis to investigate the potential correlation of metabolite concentrations and presence/severity of rash performed on study 104EU, you found that increasing levels of PZA corresponded with increasing severity of rash. As the sample size was too small and the inter-subject variability too large (from that one study) to make any conclusions about this relationship, please comment on any further work you plan to perform on investigating this issue. Please also comment on the feasibility of measuring PZA levels in plasma samples from your phase 3 studies, including all sparse PK samples and samples from the intensive PK sub-studies.

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Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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MYUNG JOO P HONG
03/14/2011

From: Hong, Myung-Joo P.
Sent: Friday, March 11, 2011 12:20 PM
To: 'Chuck_Miller@vrtx.com'
Subject: FW: Telaprevir Additional Clinical Virology Request

Hi Chuck, additional request from review team specific to Study C216:

1. Please provide by treatment group the number of subjects with rash ESI who received topical steroids, systemic steroids and oral antihistamines.
2. Please provide a discussion of any life-threatening events that occurred in the trial.
3. Please provide a discussion of dose reductions/interruptions of telaprevir, Peg-IFN and or RBV by study period (T/Pbo and overall).

Please provide responses to these and the previous requests by **COB Tuesday March 15.**

Thanks

Pat

P.S. I didn't hear anything about your response from Lisa but please submit your response listed below officially to the file.

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Thursday, March 10, 2011 2:23 PM
To: Hong, Myung-Joo P.
Subject: RE: Telaprevir Additional Clinical Virology Request

Hi Pat,
sorry it took some time to get this to you. I can include in a formal submission as well if Dr. Naeger prefers.

At this time, we have not conducted a study looking at the potential for *in vitro* antagonism of anti-HIV-1 protease inhibitors by telaprevir. However it has been demonstrated that telaprevir is not a selective inhibitor against HIV-1, *in vitro* (Module 2.6.2, Pharmacology Written Summary Section 3.8.4.1). In addition, the potential for telaprevir to interact with a panel of HIV-1 protease inhibitors has been studied in healthy volunteers (Module 2.7.2 Summary of Clinical Pharmacology Section 3.8.4.1). Finally, in the synopsis of Study VX09-950-110 provided in the NDA, no unexpected changes in HIV-1 viral load were seen at the time of the report. This observation has been confirmed at a later timepoint (slides submitted to IND 71,832 and presented at CROI 2011, not included in original NDA).

Best regards,

Chuck Miller
Director, Regulatory Affairs

Vertex Pharmaceuticals, Inc.
Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 03/10/2011 09:25 AM
Subject: RE: Telaprevir Additional Clinical Virology Request

Good Morning Chuck, Dr. Lisa Naeger wanted to know how soon she can expect to see your response?

thanks

From: Hong, Myung-Joo P.
Sent: Friday, March 04, 2011 11:22 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional Clinical Virology Request

Hi Chuck, would you provide the following information?

- Please submit a study report on combination activity relationships of telaprevir in combination with anti-HIV-1 protease inhibitors in cell culture to determine if they are antagonized by telaprevir.

Thanks
Pat

P.S. Regarding AC meeting backgrounder, please submit by March 14, 2011 as you proposed.

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MYUNG JOO P HONG
03/11/2011

From: Hong, Myung-Joo P.
Sent: Thursday, March 10, 2011 2:31 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional Request

Hi Chuck, additional request from review team:

- Please compute table of SVR24 using the snapshot at week 24 post EOT with missing replaced by LOCF and using an LOQ of 25. Specifically, subjects who were undetectable at EOT, FU Week 4 and FU Week 12 may have their last (FU Week 12) value carried forward, if missing FU Week 24. Subjects who were missing FU Week 12 values should not be included.

Thanks
Pat

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MYUNG JOO P HONG
03/10/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, March 09, 2011 3:46 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Bioanalytical Request

Hi Chuck, requests from clinical pharmacology team:

- Update on the long-term storage stability data for ethinyl estradiol in plasma from study VX06-950-007.

- Update on the long-term storage stability data for telaprevir and VRT-127394 in plasma and urine as mentioned in the following bioanalytical methods reports:



- Long-term storage stability data for tenofovir urine samples stored at -20° C for 81 days or longer in study VX-950-TiDP24-C123.

Thanks,
Pat

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/s/

MYUNG JOO P HONG
03/09/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, March 09, 2011 3:06 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional Clinical Request

Chuck, one more additional request:

For Study C216:

Please provide the outcome (SVR or no SVR) for subjects who received blood transfusions (n=39) and ESAs (n=10).

Thanks
Pat

From: Hong, Myung-Joo P.
Sent: Wednesday, March 09, 2011 2:08 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Clinical REquest

Hi Chuck, additional requests from clinical review team:

For Study C216:

- Please describe why prior breakthrough subjects were not included in the trial.
- Please provide the time to relapse for each treatment group.

Thanks
Pat

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/s/

MYUNG JOO P HONG
03/09/2011

From: Hong, Myung-Joo P.
Sent: Friday, March 04, 2011 12:47 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional Consult Request

Hi Chuck, additional request from DDDP:

- Please provide page numbers or hyperlinks (or identify their location in the study reports) to the narratives and case report forms for the following subjects:

- From study VX07-950-108: subjects 211009 and 702008

- From study VX08-950-111: subjects 111002 and 111005

We request this information by March 11, 2011.

thanks
Pat

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/s/

MYUNG JOO P HONG
03/04/2011

From: Hong, Myung-Joo P.
Sent: Thursday, March 03, 2011 2:08 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Request for Missing Bioanalytical Report

Chuck, please see the message below from Shirley.

thanks

From: Seo, Shirley
Sent: Thursday, March 03, 2011 1:56 PM
To: Hong, Myung-Joo P.; Zheng, Jenny H.
Subject: RE: Telaprevir Request for Missing Bioanalytical Report

Hi Pat,

Ok, I see that. However, now that means we are missing the report for telaprevir and VRT-127394 for that study. Please ask Vertex for the bioanalytical reports for determination of telaprevir and VRT-127394 concentrations from study VX-950-TiDP24-C122 (or point us in the direction of it if it was already submitted).

Thanks,
Shirley

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Thursday, March 03, 2011 11:43 AM
To: Hong, Myung-Joo P.
Subject: Re: Telaprevir Request for Missing Bioanalytical Report

Hi Pat,

I believe the bioanalytical report that you are looking for was included in Sequence 0011 to NDA 201,917. My colleagues at JnJ had assigned company-specific identification numbers to lopinavir and ritonavir so it was not as easy to locate as the other reports. I am including a screenshot at the bottom of my email. The Study ID in the STF is VX-950-C122-CPCD-BSS-PRD-002 and the study title is "LC-MS/MS determination of JNJ-16382028 and JNJ-26892580 in human heparin plasma samples originating from clinical trial VX-950-C122."

With respect to the second part of the question related to the freezer temperature, I have sent a query to the team and will send the response asap.



Chuck Miller
Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.

Phone: 617-444-6207
Email: Chuck_Miller@vrtx.com

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 03/03/2011 10:40 AM
Subject: Telaprevir Request for Missing Bioanalytical Report

Hi Chuck, additional request from clinical pharmacology:

- Please submit the bioanalytical reports for determination of lopinavir and ritonavir concentrations in study VX-950-TiDP24-C122 as soon as possible. Also, please clarify the freezer temperature for sample storage and stability studies for all analytes evaluated in study VX-950-TiDP24-C122.

Thanks,
Pat

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/s/

MYUNG JOO P HONG
03/03/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 2, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: March 2, 2011

NDA: 201-917/Original Submission

TO: John Weet, Ph.D.

FROM: Myung-Joo Patricia Hong, Regulatory Project Manager

SPONSOR: Vertex Pharmaceuticals, Inc.

SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Labeling

1. We have begun to review the draft telaprevir label. [REDACTED] (b) (4)
[REDACTED] According to the current guidelines for labeling, and our preference, the safety sections should be limited to information from controlled and uncontrolled Phase 3 trials. [REDACTED] (b) (4)
[REDACTED]
Please revise all the salient sections (i.e., WARNINGS, PRECAUTIONS, ADVERSE REACTIONS) to reflect outcomes of all three Phase 3 trials. Since there were no major differences noted across trials, it would be acceptable to pool data.
2. Please provide exposure multiples based on AUC where indicated. Also include justification for the basis of the calculations. Note that a comparison of exposure normalized over 24 hr is most appropriate (i.e., AUC_{0-24 hr}); however, other comparisons may be acceptable.
3. We recommend use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page.

Statistical

4. Please compute table of SVR₂₄ using the snapshot at week 24 post EOT with missing replaced by LOCF and using an LOQ of 25.

The comments above are our preliminary labeling comments and further changes should be anticipated.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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MYUNG JOO P HONG
03/02/2011



NDA 201917

**PROPRIETARY NAME REQUEST
- WITHDRAWN**

Vertex Pharmaceuticals, Inc.
130 Waverly Street
Cambridge, Massachusetts 02139

ATTENTION: John F. Weet, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) dated November 22, 2010, received November 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Telaprevir Tablets, 375 mg.

We acknowledge receipt of your February 24, 2011, correspondence, on February 24, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4), and alternate proprietary name, (b) (4). This proposed proprietary name request is considered withdrawn as of February 24, 2011.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Brantley Dorch, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Myung-Joo P. Hong at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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CAROL A HOLQUIST
03/01/2011

From: Hong, Myung-Joo P.
Sent: Thursday, February 24, 2011 9:37 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telparevir Addiitonal Data needs

Hi Chuck, the proposals you requested (in red) are acceptable. Regarding the additional variables to be added to the ADLB domain, we want for all three trials (Study 108, 111, and C216).

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Friday, February 18, 2011 2:30 PM
To: Hong, Myung-Joo P.
Subject: Re: Telparevir Addiitonal Data needs

Hi Pat,

regarding the additional variables to be added to the ADLB domain, our interpretation of this request is that it relates to Studies 108 and C216, only. Is this an accurate assumption?

In addition, we have the following comments and requests for clarification (FDA request in bold italics):

- Percent change from baseline

Vertex will add the requested variable to the datasets for Studies 108 and C216.

- Minimum on treatment measurement flag

Vertex will add the requested variable to the datasets for Studies 108 and C216. We propose to derive the minimum and maximum from the overall treatment phase (PHASEFL, see below). If there are multiple records as minimum and maximum, the first would be flagged.

- Maximum on treatment measurement flag

Please see comment regarding Minimum on treatment measurement flag above

- Phase variable (indicates which phase of the treatment the measurement was done)

The variable PHASEFL exists within the Study 108 ADLB datasets.
The two variables : TVRFL and ALLFL ndicate TVR/Pbo Treatment Phase and Overall Treatment phase.
They were used our analyses.

There is a slight difference between PHASEFL and ALLFL due to adding 30 days to the last dose date for ALLFL. Some lab records were still in the OVERALL Treatment but they were after the last dose dates, which means they are in post-treatment phase.

The table below is taken from the Study 108 define.xml file.

Are the flag variables described here sufficient for the two studies or does the reviewer have something else

(b) (4)

- Anemia AE flag (indicates if the patient had an anemia adverse event during the study - can be a composite ae)

Vertex proposes to create an anemia AE flag derived from the Anemia SSC.

- Flag to indicate low value for visit window (for instances where there is more than one measurement per visit window, provide a flag variable that identifies the lowest measurement during each treatment window)

We request clarification as to whether this flag is for one specific lab test (e.g., hemoglobin) as it specifies only a low value.

In the case of multiple values in a window that are the same, we propose to flag the value closest to the scheduled day. If equidistant from the target date, we would use the later of the two. We propose to follow in a similar fashion to the SAP, which used the centrally collected lab data.

Thank you for your consideration and clarifications,

Chuck

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 02/15/2011 11:46 AM
Subject: Telparevir Additional Data needs

Hi Chuck, we need additional items to add to the ADLB domain of the key Phase 3 clinical studies:

- Percent change from baseline
- Minimum on treatment measurement flag
- Maximum on treatment measurement flag
- Phase variable (indicates which phase of the treatment the measurement was done)
- Anemia AE flag (indicates if the patient had an anemia adverse event during the study - can be a composite ae)
- Flag to indicate low value for visit window (for instances where there is more than one measurement per visit window, provide a flag variable that identifies the lowest measurement during each treatment window)

Please let me know if you have any questions.

Thanks
Pat

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/s/

MYUNG JOO P HONG
02/24/2011



NDA 201917

GENERAL ADVICE

Vertex Pharmaceuticals, Inc.
Attention: Antoinette Paone, MS, MBA
Director, Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 26, 2011. The purpose of the meeting was to gain clarification on the information provided to support the statistical evaluation of the model for the (b)(4).

A copy of the official minutes of the meeting is attached for your information.

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

Sincerely,

{See appended electronic signature page}

Christine M. V. Moore, PhD
Deputy Director for Science and Policy
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure – meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday, January 26, 2011
TIME: 12:00 – 13:30 ET
LOCATION: FDA White Oak Facility, Building 21, Room 1537
APPLICATION: NDA 201917
DRUG NAME: telaprevir tablets

FDA ATTENDEES: (Title and Office/Division)

Sharmista Chatterjee, PhD, CMC Lead
Bogdan Kurtyka PhD, Product Quality Reviewer
Christine Moore, PhD, Deputy Director, Science and Policy
Meiyu Shen, PhD, Mathematical Statistician
Vibhakar J. Shah, Compliance Officer
Steve Miller, PhD, Branch chief
Lin Qi, PhD, Product Quality Reviewer
Yi Tsong, PhD, Deputy Director, Biometrics
Chris Hough, PhD, Product Quality Reviewer
Sandra Suarez, PhD, ONDQA/Biopharmaceutics Reviewer
Don Henry, Regulatory Project Manager

VERTEX ATTENDEES:

John Weet, Ph.D., Vice President, Regulatory Affairs
Prabu Nambiar, Ph.D., MBA, RAC, Vice President, Regulatory Affairs-CMC
Antoinette Paone, M.S., MBA, Director, Regulatory Affairs-CMC
Stephanie Krogmeier, Ph.D., Sr Manager, Regulatory Affairs-CMC
Patricia Hurter, Ph.D., Vice President, Pharmaceutical Development
Thomas Gandek, Ph.D., Sr. Director, Technical Operations
(b) (6) Statistician, Independent Consultant
Craig Dunbar, Ph.D., Sr. Director, Formulation Development
Jeffrey Katstra, M.S., Sr Scientist, Formulation Development
Eda Ross Montgomery, Ph.D., Sr. Director, Quality, CMC and QbD

BACKGROUND:

After some internal discussions pertaining to the CMC information with the application (NDA 201917, the CMC review team decided to arrange a face-to-face meeting with the applicant (Vertex) to gain clarification on the information provided to support the statistical evaluation of the model for the (b) (4). The following comments were provided to the applicant prior to the meeting to facilitate the discussion:

1 Page(s) has been Withheld in Full as B4
(CCI/TS) immediately following this page

DISCUSSION POINTS AND ACTION ITEMS:

During the meeting, Vertex presented information for each of the items listed above which will allow the CMC review team to continue the review of the application. No information requests were identified during the meeting, although two items were identified that will likely require clarification:

1. Concerns were expressed that the AMB calculation provided for the particle size distribution specification for [REDACTED]^{(b)(4)} could allow for inappropriate flexibility of the specification.
2. The language, [REDACTED]^{(b)(4)}, used for the hardness PAR equation was discussed as being unclear.

As the review team continues the evaluation, an information request may be generated to clarify the above points and other issues.

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/s/

CHRISTINE M MOORE
02/18/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, February 16, 2011 3:30 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional pharm/tox request

Hi Chuck, additional request from pharm/tox review team:

- Please indicate whether the in silico analysis for genotoxicity (mentioned on page 38 of the toxicology written summary) included (b) (4)

thanks
Pat

From: Hong, Myung-Joo P.
Sent: Wednesday, February 16, 2011 12:04 PM
To: Chuck_Miller@vrtx.com
Subject: Telaprevir pharm/tox request

Hi Chuck, the request from pharm/tox review team is:

- To help place perspective on potential drug-related effects in the low dose 13-week rat study (study no. FXU00003), please provide historical control incidence of testicular lesions detected macroscopically (small; soft) and microscopically (seminiferous tubule degeneration; diffuse germinal epithelium). Data should be matched for laboratory conducting the study, rat strain, age, etc.

thanks
Pat

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/s/

MYUNG JOO P HONG
02/16/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 14, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: February 14, 2011

NDA: 201-917/Original Submission

TO: John Weet, Ph.D.

FROM: Myung-Joo Patricia Hong, Regulatory Project Manager

SPONSOR: Vertex Pharmaceuticals, Inc.

SUBJECT: Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Clinical

1. Please provide subject narratives, case report forms, dermatology consults and biopsy reports for the following subjects from study VX07-950-108 (or identify their locations in the application if previously submitted): 129002, 152010, 214008, 214009, 703007, and 704008.
2. Please provide case report forms, dermatology consults and biopsy reports for the following subjects from study VX-950-TiDP24-C216 (or identify their locations in the application if previously submitted): AGE-0379 and NSP-0516.

Please submit this information by March 4, 2011.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MYUNG JOO P HONG
02/14/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Drug Evaluation III
Division of Reproductive and Urologic Products**

FROM (Name, Office/Division, and Phone Number of Requestor):
**Sherly Abraham, Rph
Office of Antimicrobial Products/Division of Antiviral
Products
301 796 3198**

DATE February 7, 2011	IND NO. 69,027	NDA NO. 202-258 201-917	TYPE OF DOCUMENT NME NDAs	DATE OF DOCUMENT November 10, 2010 November 23, 2010
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NAME OF DRUG Boceprevir Telaprevir	PRIORITY CONSIDERATION Priority NDA	CLASSIFICATION OF DRUG Protease Inhibitor	DESIRED COMPLETION DATE March 4, 2011
--	---	---	---

NAME OF FIRM: **Merck (previously Schering Inc.) and Vertex**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

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

COMMENTS / SPECIAL INSTRUCTIONS: **Please see the attached document for questions, tables and figures**

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

SHERLY ABRAHAM
02/07/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 4, 2011

To: John Weet, Ph.D.	From: Patricia Hong
Company: Vertex Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number:	Fax number: 301-796-9883
Phone number:	Phone number: 301-796-0807

Total no. of pages including cover: pages

Comments: NDA 201-917

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE
Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: February 4, 2011

NDA: 201-917/Original Submission

TO: John Weet, Ph.D.

FROM: Myung-Joo Patricia Hong, Regulatory Project Manager

SPONSOR: Vertex Pharmaceuticals, Inc.

SUBJECT: Advice/Information Request

Please refer to your November 23, 2010 submission submitted to NDA 201-917. We have the following comments from the review team:

Clinical Virology

1. Given the fluctuations from <10 IU/mL (BLOD) to <25 IU/mL (BLOQ) in the follow-up off-treatment samples from Studies 108 and 111, we have decided to use <25 IU/mL rather than BLOD as the cutoff value for determining SVR24 for the primary efficacy analysis. This change will only affect follow-up off-treatment samples and not on-treatment samples or treatment decision points.
2. For additional support of our decision above, please provide the following:
 - a. Please provide a comparison of the durability of SVR rates in the subjects who achieved an SVR using BLOD (<10 IU/mL) and BLOQ (<25 IU/mL) cutoffs from EXTEND Study 112. According to the study report, 122 (99.2%) of the 123 subjects who had achieved SVR following treatment with a telaprevir-based regimen maintained their SVR status out to 3 years. This SVR assessment used undetectable as cutoff. Please provide the number of subjects who maintained their SVR status if the <25 IU/mL cutoff was used to determine SVR. Please submit this information by February 11, 2011.
 - b. Please submit the data and a brief report on the reanalysis by (b) (4) of selected HCV RNA samples from Study 108 originally analyzed by (b) (4). Please let us know when these data will be submitted.

3. In the primary efficacy analysis, for those subjects who had missing SVR24 data but had data at SVR12 or follow-up time-points after SVR12, the SVR12 data or last follow-up time-point after SVR12 can be carried forward for determining SVR24.
4. Vertex may wish to reassess the primary endpoint analysis with the changes listed above for comparison with the FDA's analysis.

Statistical

5. We note that 9 subjects (108-214001, 214008, 302002, 312007, 142001, 202009, and C216-0191) had HCV RNA levels consistently <5 IU/mL during follow-up, but were not classified as achieving SVR. Please clarify why these subjects were not classified as SVR.

We are providing this above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MYUNG JOO P HONG
02/04/2011

From: Hong, Myung-Joo P.
Sent: Thursday, January 27, 2011 4:46 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telparevir. Statistical Request Clarification

Hi Chuck, the response and question from stat reviewer are:

"Vertex suggestions are fine by me. I would, however, I like to know what imputations they made when they analyzed the AE data. Did they simply pretend that AE's with the aforementioned fields missing never occurred?"

thanks

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, January 26, 2011 12:40 PM
To: Hong, Myung-Joo P.
Subject: Re: Telparevir. Statistical Request Clarification

Hi Pat,

I was just about to ask some clarifying questions related to this dataset request when you sent this email. Based on the statistical reviewer's clarifications we have some questions regarding how to treat missing values.

In general, there are missing values in a CRF and hence in the database despite a thorough data cleaning. This is due to lack of information at the site. This can be handled in various ways. For example,

- When Action Taken with respect to TVR is missing for an AE the imputed value would be 'Unknown'.
- When last intake of TVR is missing the date of W16 will be used, in case that date also is missing date of last SOC intake will be used and if also that one is missing date of last contact should be used.

The former is just reflecting missing data (Action taken) and the latter (TVR last intake date missing) is based on the rule given in the SAP if this date is missing.

The statement in the clarification email below that dosing dates are only missing for a drug never started and the action taken with respect to TVR must be one of the five alternatives listed does not reflect the data available on the CRF.

Since there are going to be cases where there is not data in the CRF, would the reviewer like us to use imputed values (and designate when a value is imputed) or delete the record entirely?

Best regards,

Chuck

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 01/25/2011 03:05 PM
Subject: Telparevir, Statistical Request Clarification

Chuck, our statistical reviewer clarified his request for the disposition of dataset and it is listed below:

One record per patient for each patient randomized and started drugs with the following fields:

1. Usubjid
2. date of first telaprevir
3. date of first ribavirin
4. date of first interferon
5. date of last telaprevir
6. date of last ribavirin
7. date of last interferon
8. reason for telaprevir stop; value of reason is 'COMPLETED' if telaprevir stopped because last scheduled dose was reached
9. reason for ribavirin stop; ditto for reaching last scheduled dose
10. reason for interferon stop; ditto for reaching last scheduled dose
11. date of last HCV measurement
12. reason for HCV measurement stop; value of reason is 'COMPLETED' if week 72 measurement has been made

Dates should be missing only a drug was never started. One would assume that this would only occur for subjects with planned delayed start of telaprevir who have toxicity or other loss to follow up in the first 12 weeks.

If a subject interrupts a drug, say for toxicity, and later resumes, that information would not be on this dataset. We want the dates of the very first and the very last dose and the date of the very last HCV measurement.

For the AE dataset, one record per AE per patient for each patient randomized and started drug with the following fields:

1. Usubjid
2. date of first dose of first drug(s) in the treatment regimen
3. start date of AE
4. stop date of AE (this can be missing if the AE is unresolved when subject is last seen)
- 5-6. Outcome of AE in character and numeric form; character value of outcome is

one of 'RESOLVED', 'RESOLVED_WITH_SEQUELAE', 'NOT_RESOLVED', or 'FATAL'. The corresponding numeric values of outcome are 1,2,3,4. Any AE that ends with death, whether or not subject is still on treatment at time of death and whether or not subject has reached or passed 72 week endpoint, is considered FATAL.

7. Serious AE, Y or N. If the stop date for a non-serious AE is not recorded and the outcome is 'NOT_RESOLVED', one would expect any analysis done with the dataset to show less concern for the Not Resolved Status than for a similar Not Resolved Serious AE.

8-9. Action taken with respect to telaprevir on AE in character and numeric form; Character Value of Action is one of the following: 'DOSE_UNCHANGED', 'DOSE_INCREASED', 'DOSE_REDUCED', 'DRUG_INTERRUPTED', 'DRUG_WITHDRAWN'.

The corresponding numeric values are 0, 1, 2, 3, 4. NOT_APPLICABLE and Missing are not acceptable value for action taken. Necessarily, the physician did one of the 5 options listed, even if the AE was considered not related to telaprevir.

10-11. Action taken with respect ribavirin

12-13. Action taken with respect to interferon.

14-16. Y or N variables for relatedness to telaprevir, ribavirin, interferon.

The fields identifying the type of AE such as AEMODIFY, AETERM, AEBODSYS, AEDECOD, AEGROUP, and so forth should also be included.

Aside from the stop date for unresolved AE's there should be no missing data in this dataset.

thanks

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]

Sent: Monday, January 24, 2011 4:36 PM

To: Hong, Myung-Joo P.

Subject: Re: Telparevir. Statistical Question

Hi Pat,

I have one initial clarification regarding the request below. Would it be safe to assume that the deliverable will be SAS datasets and a define.xml rather than a PDF containing the information?

Best regards,

Chuck

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 01/24/2011 04:21 PM
Subject: Telparevir. Statistical Question

Hi Chuck, please ask Tibotec to provide the following information:

- 1) The date of overall treatment start for every randomized subject.
 - 2) The dates of discontinuation of all treatment and of each separate drug.
 - 3) The start date, end date, outcome, and action taken for every adverse event. There should be no missing values for any of these variables for any adverse event.
 - 4) The date of trial termination for every subject who has DSTYPE= DISCONTINUED.
- thanks

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Monday, January 24, 2011 10:02 AM
To: Hong, Myung-Joo P.
Subject: Re: Telparevir. Statistical Question

Hi Pat, I have a response to the statistical question from 21 January as well as the extracted page from the C216 eCRF that is referenced in the response

Best regards,
Chuck

The DSAD is the subject disposition analysis data set, which is derived from the study drug termination page and trial termination page in eCRF. The date referring below is the start date of disposition event from the trial termination page (page 73 in eCRF attached). The date was only captured when subject lost follow up [3] or subject withdrew consent[4]. Therefore, the non-missing dates were only those subjects who terminated the study due to lost follow-up or withdrew consent. The date didn't apply to other subjects who were terminated due to other reasons.

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 01/21/2011 04:39 PM
Subject: Telparevir. Statistical Question

Hi Chuck, would you ask Tibotec to explain why the date is missing for all but 60 of the records in DSAD for trial 216?

thanks

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/s/

MYUNG JOO P HONG
01/27/2011

From: Hong, Myung-Joo P.
Sent: Tuesday, January 25, 2011 3:14 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir.Clinical Pharmacometrics Request

Hi Chuck, additional request from pharmacometrics group:

To assess the proposed virologic stopping thresholds of (b) (4) versus 1000 IU/mL at Week 4 and Week 12, you should conduct simulation studies by using the viral dynamic model in the G103 report to evaluate the following:

1. the predicted percentage (and its 90% confidence interval) of treatment naïve patients with > 1000 IU/mL HCV RNA at Week 4 and Week 12 respectively and the predicted SVR24 rate (and 90% confidence interval) for the treatment naïve patients with > 1000 IU/mL HCV RNA at Week 4 and Week 12 respectively by applying the following virologic stopping rules separately:

- a. without any stopping rule
- b. with the 1000 IU/mL stopping rules at Week 4 and Week 12 as in study

108

2. the predicted percentage (and its 90% confidence interval) of treatment naïve patients with HCV RNA levels between 100 IU/mL and 1000 IU/mL at Week 4 and Week 12 respectively and the predicted SVR24 rate (and 90% confidence interval) for the treatment naïve patients with HCV RNA levels between 100 IU/mL and 1000 IU/mL at Week 4 and Week 12 respectively by applying the following virologic stopping rules separately:

- a. with the 1000 IU/mL stopping rules at Week 4 and Week 12 as in study

108

- b. with the proposed (b) (4) stopping rules at Week 4 and Week 12

Please perform the above assessment as soon as possible within 2 weeks. Please submit your simulation codes, data files, summary tables and plots together.

Please also repeat the above assessment for prior relapsers, prior partial responders and prior null responders, and submit the simulation codes, data files, summary tables and plots within 4 weeks.

Thanks

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/s/

MYUNG JOO P HONG
01/25/2011

From: Hong, Myung-Joo P.
Sent: Friday, January 21, 2011 11:52 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional Pharmacometrics Information Request

Hi Chuck, our additional request are:

Please compare the dataset PKPD.xpt (submitted on January 14, 2011 in response to our Pharmacometrics Dataset Request on December 30, 2010) to the dataset PPAD.xpt in the iss-phase-2 and 3 fold (submitted on November 19, 2010: Rolling Submission Unit 4 - Completion of Original NDA, sequence 0005) and explain:

1. Why the data of hemoglobin worst tox grade during telaprevir phase did not match for Study 208, C216, 104, 104EU, 106, and 107 between the two datasets;
2. Why the data of rash SSC worst tox grade during telaprevir phase did not match for Study 104, 104EU, 106, and 107 between the two datasets; and
3. Please double check the dataset PKPD.xpt to make sure all of the information submitted is correct and the main analyses based on this dataset are consistent with your original study reports

Please resubmit the correct PKPD.xpt as soon as possible within 1 week.

Thanks
Pat

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/s/

MYUNG JOO P HONG
01/21/2011

1



NDA 201-917

FILING COMMUNICATION

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

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) dated November 22, 2010, received November 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for telaprevir, 375 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is May 23, 2011.

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 May 2, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Antiviral Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify telaprevir for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your requests for a waiver of pediatric studies for children less than 3 years of age and a deferral of pediatric studies in children aged 3 to less than 18 years of age for this application. Once we have reviewed your requests, we will notify you if the waiver and deferral requests are denied.

If you have any questions, call Myung-Joo Patricia Hong, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

DEBRA B BIRNKRANT
01/18/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, January 12, 2011 11:38 AM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, the response from pharmacometrics group is:

- The "LENGTH" variable is calculated based on the first day of treatment through the last day of treatment. While many trial designs are proposing response-guided therapies and have varying treatment durations between and within different arms, we ask that this field be populated with the planned maximum treatment duration from any of the treatment arms (i.e., if the study included 48 weeks of treatment enter 336). Please do not include follow-up visits when calculating the variable.

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Tuesday, January 11, 2011 4:54 PM
To: Hong, Myung-Joo P.
Subject: RE: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Good evening Pat,

I have a quick question regarding AIMS. In the STUDY dataset, there is a variable called "LENGTH". My conclusion was that this refers to the length of the study (as planned for a single patient, so the initial dose would be day 1 and the final follow-up visit would be the final day). It could also be interpreted as first subject, first dose to last subject, last dose, but I felt that this would be meaningless in the context of comparison of multiple studies as it would be highly variable.

Would you mind checking with your pharmacometricians as the intent of the LENGTH variable?

See below for the table from the AIMS spreadsheets



Chuck

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 12/30/2010 04:16 PM
Subject: RE: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, additional information request from Pharmacometrics review team is listed below.

3. A request for AIMS datasets was previously provided to the sponsor; however, these data sets were not provided with the NDA submission and are necessary for the reviewer's analyses. These data sets should be provided according to the details outlined in the attached AIMS_ControlledTerms_October.xls and AIMS_DatabaseTemplate_October.xls files. This request is in addition to the above data requests and should be submitted within one month.

thanks

From: Hong, Myung-Joo P.
Sent: Thursday, December 30, 2010 12:30 PM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, request from Pharmacometrics review team are listed below.

Please submit the following datasets and codes/scripts to evaluate population modeling and exposure-response analyses:

1. **NONMEM model control streams and output listings for Study G190 (pooled population PK report)** should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (as found in Appendices). These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
2. A dataset that includes one record per subject for subjects treated with control or T/PR in studies 104, 104EU, C208, 106, 107 (it is fine if you don't have PK prediction for this study), 108, 111 and C216 with the following information **(this should be submitted as soon as possible within 2 weeks)**:
 - a. Study ID
 - b. Unique subject ID (USUBJID)
 - c. Treatment
 - d. Important baseline factors for PK: e.g. Body weight, BMI, Sex, Race, Age, Region and others
 - e. Telaprevir CL
 - f. Telaprevir VL
 - g. Model predicted telaprevir Cmax at steady state
 - h. Model predicted telaprevir Cmin at steady state
 - i. Model predicted telaprevir AUC at steady state
 - j. Model predicted telaprevir Cavg at steady state

- k. PEG-INF concentration at day 29
- l. RBV concentration at day 29
- m. Efficacy: SVR24_{planned}, SVR week 72, SVR24_{actual}, and VBT (viral breakthrough), Relapse, RVR, eRVR, Time to first VBT (days), HCV RNA level (IU/ml) at week 2, 4, 6, 8, 10 and 12
- n. Safety: Rash_tox (SSC), Hgb_tox (SSC), Anorectal_tox (SSC), Pruritus_tox (SSC), Rash_tox (ESI: phase3), Discontinuation status, Reason for discontinuation, Time to discontinuation (day), Time to first anemia SSC event (days), Anemia event (0 or 1), Time to discontinuation due to anemia SSC (days), Anemia discontinuation event (0 or 1), Time to first onset of grade 3 rash SSC (day), rash3 event (0 or 1), Time to first onset of rash ESI (day), rash ESI event (0 or 1)
- o. Important baseline factors and HCV status for efficacy and safety: Baseline HCV RNA level (IU/mL), HCV genotype, Liver disease status, Baseline hemoglobin level, Patient prior treatment status (naïve, prior failure (nonresponders, null responders, partial responders, prior relapsers))

Thanks,

Pat

[attachment "AIMS_ControlledTerms_October.xls" deleted by Chuck Miller/BOS1/VRTX] [attachment "AIMS_DatabaseTemplate_October.xls" deleted by Chuck Miller/BOS1/VRTX]

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

/s/

MYUNG JOO P HONG
01/12/2011

From: Hong, Myung-Joo P.
Sent: Tuesday, January 11, 2011 5:03 PM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Information Request (Statistical)

Hi Chuck, additional request from statistical review team:

- Please explain the classification of the following four subjects. Notice that only one of the apparently discrepant results involves the SVR24 finding.

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

MYUNG JOO P HONG
01/11/2011

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 # 201-917	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: TBD (second name will be submitted to the NDA) Established/Proper Name: Telaprevir Dosage Form: Tablet Strengths: 375 mg		
Applicant: Vertex Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: November 22, 2010 Date of Receipt: November 23, 2010 Date clock started after UN:		
PDUFA Goal Date: May 23, 2011		Action Goal Date (if different):
Filing Date: January 21, 2011		Date of Filing Meeting: December 22, 2010
Chemical Classification: (1, 2, 3 etc.) (original NDAs only): P1		
Proposed indication(s)/Proposed change(s): In combination with peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatic C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated, including prior null responders, partial responders, and relapsers		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" 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:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
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 checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products(check combo product algorithm)

		<input type="checkbox"/> Other (drug/device/biological product)			
<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input 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 (<i>if OTC product</i>):					
List referenced IND Number(s): IND 71832					
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>		✓			
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>		✓			Second proprietary name submitted to the NDA: (b) (4) proposed
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., X 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>		✓			Priority Review
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>			✓		
If yes, explain in comment column.					
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:					
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		✓			

<u>User Fee Status</u> <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>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<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>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				✓	
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)].				✓	
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)]?					
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>					
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.fda.gov/cder/ob/default.htm All over us					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<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>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			✓		

<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 (HFD-007)</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: 5- years</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>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<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>	✓			

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)?	✓			
<i>If foreign applicant, both the applicant and the 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?	✓			
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)?	✓			
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)?	✓			
<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?	✓			

<p>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</p> <p>Note: Debarment Certification should use wording in FD&C Act 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...”</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>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)</p> <p>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</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>			✓	

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>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.</p>	✓			
<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 under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <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>		✓		Working on WR
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>	✓			(b) (4) proposed
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>	✓			
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 type="checkbox"/> Instructions for Use (IFU) <input checked="" 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 in 74-day letter.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

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 PLR format in 74-day letter.</i>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" 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>				Dermatology (12/10/10) and CDRH (12/23/10) consults requested
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of-Phase 2 meeting(s)? Date(s): CMC Meeting (EOP 2) – 3/19/2008 Clinical Meeting (Type A) – 1/16/2008 <i>If yes, distribute minutes before filing meeting</i>	✓ ✓			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 28, 2010	✓			

<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		✓		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 22, 2010

BLA/NDA/Supp #: NDA 201-917

PROPRIETARY NAME: (b) (4) (proposed)

ESTABLISHED/PROPER NAME: Telaprevir

DOSAGE FORM/STRENGTH: Tablet (375 mg)

APPLICANT: Vertex Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): In combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease including both patients who are treatment-naïve and those who have been treated previously with interferon alfa alone or in combination with ribavirin.

BACKGROUND: Vertex Pharmaceuticals, Inc. conducted two pilot clinical studies in Europe (Studies 001 and 101). Following the two pilot clinical studies and after a pre-IND interaction with the Division, IND 71832 was submitted on November, 2005. Since the development of telaprevir in the US began in 2005, there have been numerous interactions with the Division and Vertex to guide telaprevir’s development. Telaprevir was granted a “Fast Track” designation on December 7, 2007 and a rolling review ensued after receiving the first unit (pre-clinical section) on June 24, 2010. The second unit (CMC section) was submitted on July 14, 2010. Vertex Pharmaceuticals submitted the third unit (Study 108 Clinical Report) on October, 2010 and final unit on November 22, 2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Myung-Joo Patricia Hong	Y

	CPMS/TL:	Victoria Tyson	Y
Cross-Discipline Team Leader (CDTL)		Linda Lewis, M.D.	Y
Clinical	Reviewer:	Russell Fleischer	Y
	TL:	Linda Lewis	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lisa Naeger	Y
	TL:	Jules O'Rear	Y
Clinical Pharmacology	Reviewer:	Shirley Seo Shashi Amur Jiang Liu	Y Y N
	TL:	Sarah Robertson Pravin Jadhav	N Y
Biostatistics	Reviewer:	Thomas Hammerstrom	Y
	TL:	Greg Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Powley	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	George Lunn (Drug Substance)	Y
		Lin Qi (Drug Product)	N
		Bogda Kurtyka (b) (4)	Y
		Sandra Suarez-Sharp (Biopharmaceutics)	Y
		Christopher Hough (Comparability Protocol,	Y

		post-approval)	
	TL:	Stephen Miller	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Doug Campbell	Y
	TL:	Karen Takahashi	N
OSE/DMEPA (proprietary name)	Reviewer:	Walter Fava	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey Sharon Mills	Y N
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Brenda Carr (Dermatology Consult Reviewer)		N
Other attendees	Vibhakar Shah		Y
	Edward Cox		Y
	John Farley		Y
	Debra Birnkrant		Y
	Kendall Marcus		Y
	Mary Singer		Y
	Brantley Dorch		Y
	Mary Dempsey		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <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 checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input 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: April 28, 2011 <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 	<input checked="" type="checkbox"/> Not Applicable

<p>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> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" 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 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>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<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 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 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES

<p>(EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<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>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<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: DMPQ plans to do facility inspections on April, 2011</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Edward Cox, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
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"/>	<p>If priority review:</p> <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) • 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 labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>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 (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	Other

Review Milestones

Filing Date: January 21, 2011

Day 74 Deficiencies Identified Letter Date: February 5, 2011

Completion Goal Date Primary Reviews: April 25, 2011

Completion Goal Date Secondary Reviews: April 29, 2010

Completion of CDTL Review: May 2, 2011

Completion of DD Review: May 13, 2011

Action Package and Letter to OD: May 13, 2011

Completion of OD Review and sig-off: May 23, 2011

Review Meetings

Filing Meeting: December 22, 2010

GAM # 1: January 24, 2011

Mid-Cycle Meeting: February 22, 2011

GAM #2: March 22, 2011

AC Prep Meeting # 1: April 14, 2011

AC Prep Meeting # 2: April 22, 2011

PeRC Meeting: February 9, 2011

Advisory Committee Meeting: April 28, 2011

Appears this way on original

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/s/

MYUNG JOO P HONG
01/11/2011

From: Tran, Paul
Sent: Monday, January 10, 2011 1:25 PM
To: 'Chuck_Miller@vrtx.com'
Cc: Hong, Myung-Joo P.; Reese, Cicely
Subject: Letter to the Sponsor for upcoming April 28, 2011 FDA Advisory Committee Meeting

Importance: High

Attachments: Sponsor letter AVDAC April 28, 2011 Vertex.pdf; Sponsor Timeline April 28, 2011 Telaprevir (Vertex).pdf

Dear Dr. Miller,

My name is Paul Tran; I am the Designated Federal Official for the FDA Antiviral Drugs Advisory Committee. Attached are the timeline and the Letter to the Sponsor informing you of some important due dates for the FDA Antiviral Drugs Advisory Committee meeting tentatively scheduled for April 28, 2011 to discuss NDA 201-917, Telaprevir.

Please review the timeline and Letter to the Sponsor and let me know if you have any questions or concerns. I look forward to working with you on this advisory committee meeting in April.



Sponsor letter
AVDAC April 28,...



Sponsor Timeline
April 28, 201...

Warmest Regards,
Paul

Paul Tran, R.Ph
Health Science Administrator
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Advisory Committee and Consultant Management (DACCM)
Office of Executive Programs
10903 New Hampshire Avenue
WO/31-2404
Silver Spring, MD 20993-0002
Phone: 301-796-9029
Fax: 301-847-8540
Email: Paul.Tran@fda.hhs.gov



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Chuck Miller
Associate Director, Regulatory Affairs
Vertex Pharmaceuticals, Inc.
130 Waverly Street
Cambridge, MA 02139

January 10, 2011

Dear Dr. Miller:

We are in the process of developing the Agenda for the upcoming meeting of the Antiviral Drugs Advisory Committee, which is tentatively scheduled for April 28, 2011. The committee will discuss (NDA) 201-917, Telaprevir, manufactured by Vertex Pharmaceuticals, Inc. The session is expected to begin at 8:00 a.m.

Please note that the Federal Register Notice for this meeting has not yet been made publicly available and information pertaining to this meeting is not publicly releasable until that time. You may check to see if the FR notice is published by checking the web site: <http://www.gpoaccess.gov/fr/> In the Quick Search Box, type: Antiviral Drugs Advisory Committee.

A timeline of significant due dates in the preparation for the advisory committee meeting is attached.

Prior to the meeting:

1) **List of Investigators:** Please forward to me an electronic copy of the list of investigators for all trials supporting the application(s) under review by February 10, 2011.

2) Preparation and Submission of background materials for the meeting:

We are currently following the deadlines and instructions listed in the August 2008 Guidance for Industry "Advisory Committee Meetings — Preparation and Public Availability of Information Given to Advisory Committee Members". The link to the document may be found on the following URL address:

<http://www.fda.gov/oc/advisory/GuidancePolicyRegs/AC48HourFINALGuidance080408.pdf>

Most of the Advisory Committee Members will be receiving the electronic copies of the background material on CDs. Please provide 35 electronic copies in Microsoft Word/Adobe PDF on separate CDs (in separate cases to protect them during mailing) and 12 of paper copies of your background package. These copies must be received by me no later than March 29, 2011 by closed of business at 5 p.m. (22 business days prior to the meeting).

The package delivery (FedEx, UPS) address is:

Division of Advisory Committee and Consultant Management (DACCM)
Food and Drug Administration
CDER, OEP
10903 New Hampshire Avenue
White Oak, Building 31- Room 2419
Silver Spring, MD 20993-0002
(Main Phone: 301-796-9001)

Please be sure that the copies, both paper and electronic, are marked “AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION” as described in the Guidance, and that all CONFIDENTIAL markings in the headers, footers or watermarks of the pages, or the labels of the CDs, have been completely removed. I will then forward the copies to the Committee, the Division of Information Disclosure Policy, and to the reviewing divisions.

3) Meeting Participants

As soon as possible, please provide a preliminary list of all of the presenters and responders who will be representing you at the meeting, along with their affiliation. Representational activities include presenting, responding to questions, and sitting in the sponsor section at the meeting. Please send your final version of this list to me no later than April 13, 2011.

Please note that any current or former Advisory Committee members, or other past or present Special Government Employees, who will be attending the meeting with you will be asked to complete the procedures in MaPP 6001.1 “Special Government Employees Representing Sponsors Before CDER” (<http://www.fda.gov/cder/mapp/6001-1.pdf>), and should start this process as soon as possible. The goal is to avoid situations in which a former member and/or consultant might inadvertently violate the law concerning representational activities.

It is a violation of ethics statutes 18 USC 203 and 205 for a Federal Employee, including employees of the NIH, CDC and VA, to represent a third party before another agency. Please note that Federal employees, including employees of the NIH, CDC and VA, will not be permitted to represent your company at the meeting.

The Committee Chair will be asking that each of your speakers (both presenters and responders), not employed by your company, advise the Committee of any financial relationships that they may have with your company, such as consulting fees, travel expenses, honoraria, and other interests, including equity interests and those based upon the outcome of the meeting.

4) Final Agenda

I will also need to know the names and affiliations of your planned speakers and the titles of their presentations as soon as this information is available. Information received by April 13, 2011 will be included in the Final Agenda for the meeting.

Meeting Day Materials

Please bring with you to the meeting at least 40 paper copies of any slides that will be presented at the meeting for use by the Committee members. At the end of the meeting day, we ask that you provide an electronic version of your slide presentations in Adobe Version 8 or higher. If back-up slides are presented, we ask that you also provide these on CD at the conclusion of the advisory committee meeting. The slides will be also posted on the FDA website after the meeting. The Guidance also encourages sponsors to bring a “reasonable number” of hard copies of the presentation slides for distribution to the public.

I am the Designated Federal Officer for the committee and look forward to working with you. Please contact me at (301) 796-9029 if you have any questions or concerns.

Thank you,

Paul Tran, R.Ph
Health Science Administrator
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Advisory Committee and Consultant Management (DACCM)
Office of Executive Programs
10903 New Hampshire Avenue
WO/31-2404
Silver Spring, MD 20993-0002
Phone: 301-796-9029
Fax: 301-847-8540
Email: Paul.Tran@fda.hhs.gov

AC meeting Date ----- ->		4/28/2011	
AC meeting Topic ---- ->		Telaprevir (201-917)	
AC meeting Timeline:			
# Business Days before AC meeting	Date:	Action:	Notes
22	03/29/11	Sponsor Package due to ACS (Fully Releasable) Final and Complete Sponsor Background package due to ACS	
21	03/30/11	Final and Complete Sponsor Background sent to Committee and Division	
14	04/08/11	Redacted CDER Review Division Background Package sent to Sponsor	
(15 CD)	04/13/11	<input type="checkbox"/> FDA Dockets posts waivers onto the web. (15 calendar days)	
8	04/18/11	Final discussion with Sponsor on redaction of exempt materials from CDER package will be completed.	
2	04/26/11	Sponsor package and redacted CDER package are posted on FDA website	
0	04/28/11	AC meeting day.	

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/s/

MYUNG JOO P HONG
01/10/2011

From: Hong, Myung-Joo P.

Sent: Monday, January 10, 2011 1:42 PM

To: 'Chuck_Miller@vrtx.com'

Subject: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, additional information request from Pharmacometrics review team is listed below.

- Based on your 12/20/2010 submission to IND 71832, treatment-naive subjects in trials 104 and 108 were genotyped for IL28B polymorphisms. Please submit these data and analyses along with the data requested in our previous e-mail to you dated 12/15/2010.

Thanks,

Pat

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/s/

MYUNG JOO P HONG
01/10/2011

From: Hong, Myung-Joo P.
Sent: Thursday, January 06, 2011 2:08 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Stat Question

Hi Chuck, our stat reviewer likes to know:

- Why, in trial 108, there are typically four HCV measurements per date per subject and why often they are all the same but in several 100 cases, they are different?

thanks
Pat

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/s/

MYUNG JOO P HONG
01/06/2011

From: Hong, Myung-Joo P.
Sent: Thursday, January 06, 2011 10:08 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir QT Study Report Request

Attachments: HighlightsofClinicalPharmacology.doc

Hi Chuck, additional request for QT Study Report.

- In addition to the clinical pharmacology table, please provide us a dataset with estimated slopes (b hat) of each subject for QTc Individual linear and QTc Individual nonlinear. Also, please include the slopes of QTc linear and QTc non linear in the dataset.

thanks
Pat

From: Hong, Myung-Joo P.
Sent: Wednesday, January 05, 2011 4:33 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir QT Study Report Request

Hi Chuck, please fill out the attached table and submit to the file ASAP. thanks

Pat

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/s/

MYUNG JOO P HONG
01/06/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, January 05, 2011 11:30 AM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)
Hi Chuck, our responses (Black and bold) are below.

thanks
Pat

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Wednesday, January 05, 2011 10:12 AM
To: Hong, Myung-Joo P.
Subject: RE: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Pat,

our team has met to plan how we can fulfill the Clinical Pharmacometrics Information requests. I have sorted the requests numerically with our updates and questions (in *Blue Bold Italics*) back to the Division as follows:

1. NONMEM model control streams and output listings for **Study G190 (pooled population PK report)** should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (as found in Appendices). These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Vertex update: We are preparing these files now and will include them with our planned submission this Friday (which will include the requested HLA and Study 021 datasets from December)

FDA response: Thank you very much! We appreciate your quick action.

2. A dataset that includes one record per subject for subjects treated with control or T/PR in studies 104, 104EU, C208, 106, 107 (it is fine if you don't have PK prediction for this study), 108, 111 and C216 with the following information (**this should be submitted as soon as possible within 2 weeks**):
- a. Study ID
 - b. Unique subject ID (USUBJID)
 - c. Treatment
 - d. Important baseline factors for PK: e.g. Body weight, BMI, Sex, Race, Age, Region and others
 - e. Telaprevir CL
 - f. Telaprevir VL
 - g. Model predicted telaprevir Cmax at steady state
 - h. Model predicted telaprevir Cmin at steady state
 - i. Model predicted telaprevir AUC at steady state
 - j. Model predicted telaprevir Cavg at steady state
 - k. PEG-INF concentration at day 29
 - l. RBV concentration at day 29
 - m. Efficacy: SVR24_{planned}, SVR week 72, SVR24_{actual}, and VBT (viral breakthrough), Relapse, RVR, eRVR, Time to first VBT (days), HCV RNA level (IU/ml) at week 2, 4, 6, 8, 10 and 12
 - n. Safety: Rash_tox (SSC), Hgb_tox (SSC), Anorectal_tox (SSC), Pruritus_tox (SSC), Rash_tox (ESI: phase3), Discontinuation status, Reason for discontinuation, Time to discontinuation (day), Time to first anemia SSC event (days), Anemia event (0 or 1), Time to discontinuation due to anemia SSC (days),

Anemia discontinuation event (0 or 1), Time to first onset of grade 3 rash SSC (day), rash3 event (0 or 1), Time to first onset of rash ESI (day), rash ESI event (0 or 1)

o. Important baseline factors and HCV status for efficacy and safety: Baseline HCV RNA level (IU/mL), HCV genotype, Liver disease status, Baseline hemoglobin level, Patient prior treatment status (naïve, prior failure (nonresponders, null responders, partial responders, prior relapsers)

Vertex Question:

In Item "n", for the SSC would you like a grading or would you like us to use a cutoff (e.g., grade 2 or higher for Anemia_tox, Anorectal_tox...grade 3 for Rash_tox (ESI: phase 3)?

- FDA response: Thanks. We would like a grading SSC.

Also for Item "n", for safety, we propose to look at telaprevir/placebo phase only. Is this acceptable?

- FDA response: The telaprevir/placebo phase is our main focus, but additional columns for the overall phase should be also included.

For time to discontinuation of anemia, we propose to use the criteria that was used for the studies (e.g., Phase 2 studies would use discontinuation of all study drugs; Phase 3 studies would use discontinuation of telaprevir AND discontinuation of all study drugs).

- FDA response: Acceptable.

3. A request for AIMS datasets was previously provided to the sponsor; however, these data sets were not provided with the NDA submission and are necessary for the reviewer's analyses. These data sets should be provided according to the details outlined in the attached AIMS_ControlledTerms_October.xls and AIMS_DatabaseTemplate_October.xls files.

- FDA Response: This request is in addition to the above data requests and should be submitted within one month.

Vertex Question: We appreciate the reviewer's request for the AIMS datasets. As we had previously understood that the AIMS database was geared towards programs in earlier development rather than for NDA review, this will be a considerable undertaking given the schedule and potential scope of data from the telaprevir program. We will make every attempt to provide them in a timely fashion. We would appreciate the following clarifications:

Which studies the reviewer would like to have in the AIMS format?

In which order they would like to receive the studies?

- FDA response: Study 108, C216, 111, 104, 104EU, 106, 208, 107 (in the order we wish to receive).

We are prepared to provide them on a study-by-study basis as they are completed so that time is not lost for the reviewer.

- FDA Response: It is acceptable. We appreciate your effort.

Best regards,

Chuck

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>

To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 12/30/2010 04:16 PM
Subject: RE: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, additional information request from Pharmacometrics review team is listed below.

3. A request for AIMS datasets was previously provided to the sponsor; however, these data sets were not provided with the NDA submission and are necessary for the reviewer's analyses. These data sets should be provided according to the details outlined in the attached AIMS_ControlledTerms_October.xls and AIMS_DatabaseTemplate_October.xls files. This request is in addition to the above data requests and should be submitted within one month.

thanks

From: Hong, Myung-Joo P.
Sent: Thursday, December 30, 2010 12:30 PM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, request from Pharmacometrics review team are listed below.

Please submit the following datasets and codes/scripts to evaluate population modeling and exposure-response analyses:

1. **NONMEM model control streams and output listings for Study G190 (pooled population PK report)** should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (as found in Appendices). These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
2. A dataset that includes one record per subject for subjects treated with control or T/PR in studies 104, 104EU, C208, 106, 107 (it is fine if you don't have PK prediction for this study), 108, 111 and C216 with the following information **(this should be submitted as soon as possible within 2 weeks)**:
 - a. Study ID
 - b. Unique subject ID (USUBJID)
 - c. Treatment
 - d. Important baseline factors for PK: e.g. Body weight, BMI, Sex, Race, Age, Region and others
 - e. Telaprevir CL
 - f. Telaprevir VL
 - g. Model predicted telaprevir Cmax at steady state
 - h. Model predicted telaprevir Cmin at steady state

- i. Model predicted telaprevir AUC at steady state
- j. Model predicted telaprevir Cavg at steady state
- k. PEG-INF concentration at day 29
- l. RBV concentration at day 29
- m. Efficacy: SVR24_{planned}, SVR week 72, SVR24_{actual}, and VBT (viral breakthrough), Relapse, RVR, eRVR, Time to first VBT (days), HCV RNA level (IU/ml) at week 2, 4, 6, 8, 10 and 12
- n. Safety: Rash_tox (SSC), Hgb_tox (SSC), Anorectal_tox (SSC), Pruritus_tox (SSC), Rash_tox (ESI: phase3), Discontinuation status, Reason for discontinuation, Time to discontinuation (day), Time to first anemia SSC event (days), Anemia event (0 or 1), Time to discontinuation due to anemia SSC (days), Anemia discontinuation event (0 or 1), Time to first onset of grade 3 rash SSC (day), rash3 event (0 or 1), Time to first onset of rash ESI (day), rash ESI event (0 or 1)
- o. Important baseline factors and HCV status for efficacy and safety: Baseline HCV RNA level (IU/mL), HCV genotype, Liver disease status, Baseline hemoglobin level, Patient prior treatment status (naïve, prior failure (nonresponders, null responders, partial responders, prior relapsers))

Thanks,

Pat

[attachment "AIMS_ControlledTerms_October.xls" deleted by Chuck Miller/BOS1/VRTX] [attachment "AIMS_DatabaseTemplate_October.xls" deleted by Chuck Miller/BOS1/VRTX]

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/s/

MYUNG JOO P HONG
01/05/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, January 05, 2011 4:33 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir QT Study Report Request

Attachments: HighlightsofClinicalPharmacology.doc
[Hi Chuck, please fill out the attached table and submit to the file ASAP. thanks](#)

[Pat](#)

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
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/s/

MYUNG JOO P HONG
01/05/2011

REQUEST FOR CONSULTATION

TO (Office/Division): IRT

FROM (Name, Office/Division, and Phone Number of Requestor):
Myung-Joo Patricia Hong/RPM/OAP/DAVP
796-0807

DATE
1/4/11

IND NO.

NDA NO.
201-917

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
11/23/10

NAME OF DRUG
telaprevir

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Antiviral

DESIRED COMPLETION DATE
2/28/11

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 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 checked="" 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: Please review additional ECG monitoring study performed per our comments faxed on 5/8/08. The faxed comments are attached below and the study report can be found in the submission folder under section 5.3.4 "Reports of Human Pharmacodynamic (PD) Studies." It is Study VX-950-TiDP24-C136. The link to the submission:

EDR Location: \\CDSESUB1\EVSPROD\NDA201917\201917.enx

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Antimicrobial Products
Division of Antiviral Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 8, 2008

To: Eric Ruby	From: Victoria Tyson-Medlock Division of Antiviral Products
Company: Vertex Pharmaceuticals, Incorporated	Title: Regulatory Project Manager
Fax number: (617) 444-6803	Fax number: 301-796-9885
Phone number: (617) 444-6133	Phone number: 301-796-0827

Subject: Comments based on review of the thorough QT study VX06-950-008

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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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Date: May 8, 2008
IND: 71, 832
Drug: VX-950
To: Eric Ruby
Sponsor: Vertex Pharmaceuticals, Incorporated
From: Victoria Tyson-Medlock, Regulatory Project Manager
Through: Russell Fleischer, M.P.H., PA-C, Medical Officer
Concurrence: Linda Lewis, M.D., Medical Team Leader
Subject: IND: 71, 832 SN 226 and 247

Please refer to your IND 71, 832, VX-950 for the treatment of patients with genotype 1 chronic hepatitis C and the October 24, 2007, submission, SN 226, that consists of the QT study VX06-950-008, entitled "A Phase 2, Randomized, Placebo-Controlled, Crossover Study of the Effect of VX-950 on QT Intervals in Healthy Male Subjects." We also refer to the revised datasets for this study submitted on December 27, 2007, SN 247. We have reviewed this study and have the following comments and recommendations:

Clinical Information:

The maximum exposures achieved in this study may not be sufficient to cover increases in plasma concentration expected due to moderate or severe hepatic impairment and know drug-drug interaction such as:

- the maximum enzyme inhibition following multiple dose of ketoconazole in combination with VX-950; and
- 2.2-fold increase in maximum exposure following co-administration of ritonavir.

Therefore, we recommend additional ECG monitoring in clinical studies enrolling patients with hepatic impairment or on concomitant potent CYP3A4 inhibitors.

We are providing this above information via telephone facsimile for your convenience.
THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.
Please feel free to contact me at 301-796-1500 if you have any questions regarding the contents of this transmission.

Victoria Tyson-Medlock
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

Linked Applications

Sponsor Name

Drug Name

IND 71832

VERTEX PHARMS

VX-950

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/s/

VICTORIA L TYSON MEDLOCK

05/08/2008

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/s/

MYUNG JOO P HONG
01/04/2011

From: Hong, Myung-Joo P.
Sent: Thursday, December 30, 2010 4:16 PM
To: 'Chuck_Miller@vrtx.com'
Subject: RE: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Attachments: AIMS_ControlledTerms_October.xls; AIMS_DatabaseTemplate_October.xls

Hi Chuck, additional information request from Pharmacometrics review team is listed below.

3. A request for AIMS datasets was previously provided to the sponsor; however, these data sets were not provided with the NDA submission and are necessary for the reviewer's analyses. These data sets should be provided according to the details outlined in the attached AIMS_ControlledTerms_October.xls and AIMS_DatabaseTemplate_October.xls files. This request is in addition to the above data requests and should be submitted within one month.



AIMS_ControlledTer AIMS_DatabaseTe
ms_October.x... mplate_October....

thanks

From: Hong, Myung-Joo P.
Sent: Thursday, December 30, 2010 12:30 PM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Information Request (Clinical Pharmacometrics)

Hi Chuck, request from Pharmacometrics review team are listed below.

Please submit the following datasets and codes/scripts to evaluate population modeling and exposure-response analyses:

1. NONMEM model control streams and output listings for **Study G190 (pooled population PK report)** should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (as found in Appendices). These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
2. A dataset that includes one record per subject for subjects treated with control or T/PR in studies 104, 104EU, C208, 106, 107 (it is fine if you don't have PK prediction for this study), 108, 111 and C216 with the following information (**this should be submitted as soon as possible within 2 weeks**):
 - a. Study ID

- b. Unique subject ID (USUBJID)
- c. Treatment
- d. Important baseline factors for PK: e.g. Body weight, BMI, Sex, Race, Age, Region and others
- e. Telaprevir CL
- f. Telaprevir VL
- g. Model predicted telaprevir Cmax at steady state
- h. Model predicted telaprevir Cmin at steady state
- i. Model predicted telaprevir AUC at steady state
- j. Model predicted telaprevir Cavg at steady state
- k. PEG-INF concentration at day 29
- l. RBV concentration at day 29
- m. Efficacy: SVR24_{planned}, SVR week 72, SVR24_{actual}, and VBT (viral breakthrough), Relapse, RVR, eRVR, Time to first VBT (days), HCV RNA level (IU/ml) at week 2, 4, 6, 8, 10 and 12
- n. Safety: Rash_tox (SSC), Hgb_tox (SSC), Anorectal_tox (SSC), Pruritus_tox (SSC), Rash_tox (ESI: phase3), Discontinuation status, Reason for discontinuation, Time to discontinuation (day), Time to first anemia SSC event (days), Anemia event (0 or 1), Time to discontinuation due to anemia SSC (days), Anemia discontinuation event (0 or 1), Time to first onset of grade 3 rash SSC (day), rash3 event (0 or 1), Time to first onset of rash ESI (day), rash ESI event (0 or 1)
- o. Important baseline factors and HCV status for efficacy and safety: Baseline HCV RNA level (IU/mL), HCV genotype, Liver disease status, Baseline hemoglobin level, Patient prior treatment status (naïve, prior failure (nonresponders, null responders, partial responders, prior relapsers)

Thanks,

Pat

42 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MYUNG JOO P HONG
01/06/2011

From: Hong, Myung-Joo P.
Sent: Wednesday, December 22, 2010 7:53 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional missing items from Clinical Pharm group
Hi Chuck, please submit the missing items that did not arrive in the last submission from Vertex:

1. We received your submission of bioanalytical reports for studies VX-950-TiDP24-C121, VX-950-TiDP24-C123, VX-950-TiDP24-C124, VX-950-TiDP24-C130, VX-950-TiDP24-C132, VX-950-TiDP24-C133, VX-950-TiDP24-C134, VX-950-TiDP24-C135, VX-950-TiDP24-C208 as previously communicated to you. However, for studies VX-950-TiDP24-C123 and VX-950-TiDP24-C135, we did not receive the bioanalytical report for the determination of VX-950 and VRT-127394 in human plasma samples. (You submitted the reports for the interacting drugs only.) Please submit the reports for VX-950 and VRT-127394 for these two studies.
2. We received your submission of PK concentration and parameter datasets for studies VX-950-TiDP24-C122, VX-950-TiDP24-C124, VX-950-TiDP24-C130, VX06-950-106, VX-950-TiDP24-C208. However, we did not receive the datasets for study VX09-950-021. Please submit PK concentration and parameter datasets for VX-950, cyclosporine, and tacrolimus in study VX09-950-021.

thanks

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/s/

MYUNG JOO P HONG
12/22/2010

From: Hong, Myung-Joo P.
Sent: Wednesday, December 22, 2010 11:44 AM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir Additional Virology Request

Hi Chuck, additional request from virology group:

- Please determine the number of fluctuations and rate of fluctuation (percentage of subjects with fluctuation) from 5 IU/mL (<10 BLOD) to 17.5 IU/mL (<25 BLOQ but detectable) back to 5 IU/mL after treatment during follow-up in Study 108, Study 111 and Study 216.

- We have noted that different vendors were used for HCV viral load analysis in the Studies 108/111 and Study 216. Please provide an explanation for the variability in viral load fluctuation from BLOD and BLOQ following treatment in the different studies with a report from (b) (4) laboratories on possible reasons for the viral load fluctuations between BLOD and BLOQ in Studies 108 and 111.

thanks

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/s/

MYUNG JOO P HONG
12/22/2010

Subject: NDA 201-917 Telaprevir Clinical Virology Information Request

From: Min, Stacey
Sent: Thursday, December 16, 2010 12:32 PM
To: 'Chuck_Miller@vrtx.com'
Subject: NDA 201-917 Telaprevir Clinical Virology Information Request

Dear Chuck,

We have a request regarding your NDA 201-917 for telaprevir.

Please confirm which central laboratory/vendor was responsible for HCV RNA viral load quantification in each of the Phase III studies: Studies 108, 111, and 216.

Please submit this information to the NDA as soon as possible.

Thank you,
Stacey

Stacey Min, PharmD
Regulatory Project Manager
FDA\CDER\OND\Division of Antiviral Products
10903 New Hampshire Ave.
Silver Spring, MD 20993
Building 22, Room 6315
Phone: 301-796-4253
Fax: 301-796-9883
stacey.min@fda.hhs.gov

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/s/

MYUNG JOO P HONG
12/16/2010

From: Hong, Myung-Joo P.
Sent: Wednesday, December 15, 2010 6:30 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir datasets

Hi Chuck, please provide the following datasets:

1. Dataset(s) associated with the Clinical Study Report: IL28B Polymorphisms (C216-il28b.pdf) that contains IL28B genotype data, demographic information, primary and secondary efficacy endpoint data in all the arms of study C216 (VX-950-TiDP24-C216) from 527 subjects.

2. Dataset(s) associated with the Pharmacology Report (g201) that contains HLA allele information, demographic information and rash severity data (mild, moderate and severe) from 187 subjects from the VX05-950-104, VX05-950-104EU, VX07-950-108, VX08-950-111 clinical trials.

Thanks
Pat

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/s/

MYUNG JOO P HONG
12/15/2010

From: Hong, Myung-Joo P.
Sent: Wednesday, December 15, 2010 12:37 PM
To: 'Chuck_Miller@vrtx.com'
Subject: Telaprevir datasets
[Hi Chuck, our stat reviewer mentioned that "Trials 111 and 108 are fine the way they are."](#)

[thanks](#)

From: Chuck_Miller@vrtx.com [mailto:Chuck_Miller@vrtx.com]
Sent: Tuesday, December 14, 2010 3:53 PM
To: Hong, Myung-Joo P.
Subject: Re: Datasets

Hi Pat,

we are working through this request. We do, however, have some questions related to the request as follows:

General) The request seems to be based on Study C216 variables. Would you like us to create these datasets for Studies 108 and 111? If this is the case, there will be certain circumstances where some variables may not apply or other variables may be more appropriate, given the different studies.

Dataset #2)

a) Regarding the Variables SVRASNS (Planned and Actual). As this seems to be based on Study C216, it should be noted if you would like datasets from Studies 108 and 111, different sensitivity analyses would apply. A sensitivity analysis performed for Study C216 called for the use of local labs if a central lab was missing. As it turned out, there were no local labs therefore the sensitivity analysis was the same as the SVR(planned) or SVR(actual). There are other sensitivity analyses that were applicable only to Studies 108 and 111. Please advise as to which sensitivity analysis or analyses you would like to see used in this dataset.

b) Regarding variable SVRPLOCF: In Study C216, the only LOCF analysis that was performed applied to the placebo arm. In the C216 placebo arm only, if a subject discontinued early at any time point, the last observation was carried forward for this sensitivity analysis. This resulted in a potential conservative bias in favor of placebo (e.g., if a subject discontinued on the 6th week of placebo/PR treatment and did not return for the SVR24 timepoint many months later, they were considered a success in this analysis if they were undetectable on the study week 6 visit). For Studies 108 and 111, an LOCF analysis was defined that only applied to the week 12 follow-up visit (e.g., "SVR12" carried forward).

Would you like to see a common SVRPLOCF variable applied to a specific follow-up timepoint or timepoints from all three studies (e.g. planned follow-up week 4 and/or follow-up week 12) or from any on-treatment value as well?

If you would like to convene a brief call with a small clinical team (stats, programming, and medics) to clarify, we could do that as well.

Best regards,

Chuck

From: "Hong, Myung-Joo P." <Myung-Joo.Hong@fda.hhs.gov>
To: "Chuck_Miller@vrtx.com" <Chuck_Miller@vrtx.com>
Date: 12/10/2010 10:11 PM
Subject: Datasets

Chuck, additional request..... Please re-submit two datasets.

1. One should contain one record per visit per subject with the following fields: arm, subject id, date of visit, day of visit relative to start of therapy, HCV measurement on the visit, label for type of visit, similar to ANALTPT and VISIT.
2. The second data set should contain one record per subject with the following fields: arm, subject id, the results of each of the different analyses for SVR: including

SVR24C SVR CATEGORY 24 WKS AFTER PLANNED EOT

SVR24SC SVR SUBCATEGORY 24 WKS AFTER PLANNED EOT

VLCAT OUTCOME CATEGORY

SVRAVFF SVR ACTUAL OVERRULED VF FLAG

SVRPVFF SVR PLANNED OVERRULED VF FLAG

SVRA SVR ACTUAL

SVRASNS SVR ACTUAL (SENSITIVITY ANALYSIS)

SVRP SVR PLANNED

SVRPLOCF SVR PLANNED LOCF

SVRPSNS SVR PLANNED (SENSITIVITY ANALYSIS)

None of the fields listed above should have been included in the dataset with one record per visit.

thanks
Pat

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/s/

MYUNG JOO P HONG
12/15/2010

From: Hong, Myung-Joo P.
Sent: Monday, December 13, 2010 4:03 PM
To: 'Chuck_Miller@vrtx.com'
Cc: Robertson, Sarah; Seo, Shirley
Subject: Telaprevir--missing items

Hi Chuck, we were not able to locate or access the following reports and datasets:

Bionanalytical reports for studies:

VX-950-TiDP24-C121
VX-950-TiDP24-C123
VX-950-TiDP24-C124
VX-950-TiDP24-C130
VX-950-TiDP24-C132
VX-950-TiDP24-C133
VX-950-TiDP24-C134
VX-950-TiDP24-C135
VX-950-TiDP24-C208

PK concentration and parameter datasets for studies:

VX-950-TiDP24-C122
VX-950-TiDP24-C124
VX-950-TiDP24-C130
VX09-950-021
VX06-950-106
VX-950-TiDP24-C208

Please submit these files prior to the filing date of your application or let us know whether it is hidden in the submission.

Thanks
Pat

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/s/

MYUNG JOO P HONG
12/13/2010

REQUEST FOR CONSULTATION

TO (Office/Division): ODE III/Division of Dermatology and
Dental Products

FROM (Name, Office/Division, and Phone Number of Requestor):
Myung-Joo Patricia Hong, RPM, OAP/DAVP
301-796-0807

DATE
Dec. 10, 2010

IND NO.

NDA NO.
201-917

TYPE OF DOCUMENT
New NDA Submission

DATE OF DOCUMENT
Nov. 23, 2010

NAME OF DRUG
Telaprevir

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Antiviral

DESIRED COMPLETION DATE
April 4, 2011

NAME OF FIRM:

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 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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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|---|---|
| <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

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| <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: Telaprevir is a NS3/4 protease inhibitor developed for treatment of chronic hepatitis C virus infection. The drug is administered for up to 12 weeks in combination with pegylated interferon and ribavirin. During development, it was noted that telaprevir caused rash and pruritis that in some cases was severe and treatment limiting. The Applicant devised a special search criteria to evaluate the safety data base for rash and pruritis. In addition, they established a category of events of special interest to capture Grade 3 and 4 rash, discontinuations due to rash and cases of Stevens Johnson Syndrome; which there were a few. The Applicant convened a Dermatology Expert Panel to evaluate clinical cases, photographs and skin biopsies. Additionally, the Applicant states they have attempted to investigate the mechanism of the rash but have not found anything definitive. The pivotal trials for this NDA are Studies 108 and C216. The Expert Panel review with photos are in Section 5.3.5.3 of the NDA. Biopsy slides have been requested.

SIGNATURE OF REQUESTOR

Myung-Joo Patricia Hong
Reference ID: A2875794

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

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PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

MYUNG JOO P HONG
12/10/2010



NDA 201-917

NDA ACKNOWLEDGMENT

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

Dear Dr. Weet:

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: Telaprevir, Tablet, 375 mg

Date of Application: November 22, 2010

Date of Receipt: November 23, 2010

Our Reference Number: NDA 201-917

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 DATE 60 DAYS FROM DATE OF RECEIPT OF APPLICATION, 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 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/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/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://prinfo.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 201-917**, submitted on November 22, 2010, 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 Antiviral 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 Myung-Joo Patricia Hong, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

MYUNG-JOO PATRICIA HONG, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MYUNG JOO P HONG
12/03/2010

REQUEST FOR CONSULTATION

TO (Division/Office):

CDER OSE CONSULTS

FROM: Myung-Joo Patricia Hong

DATE December 3, 2010	IND NO.	NDA NO. 201-917	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT November 23, 2010
NAME OF DRUG Telaprevir	PRIORITY CONSIDERATION Priority Review by May 23, 2011	CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE April 1, 2011	

NAME OF FIRM:

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 II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Proprietary name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <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 IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
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| <input type="checkbox"/> PHASE IV 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"/> PRECLINICAL |
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COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor submitted a new NDA application for telaprevir. Telaprevir, in combination with peginterferon alfa and ribavirin, is being proposed for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease including both patients who are treatment naïve and those who have been treated previously with interferon alfa alone or in combination with ribavirin. Vertex proposed (b) (4) as a proprietary name.

Please review proposed proprietary name (b) (4).

PDUFA DATE: May 23, 2011

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival NDA 201-917

HFD-530/Division File

HFD-530/Myung-Joo Patricia Hong

HFD-530/USP/Reichen/Linda Lewis

Reference ID: 2871936

EDR Location: \\CDSESUB1\EVSPROD\NDA201917\201917.enx

NAME AND PHONE NUMBER OF REQUESTER

Myung-Joo Patricia Hong, 301-796-0807

METHOD OF DELIVERY (Check one)

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5/28/05

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/s/

MYUNG JOO P HONG
12/03/2010

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MYUNG JOO P HONG
12/03/2010



NDA 201917

INFORMATION REQUEST

Vertex Pharmaceuticals, Inc.
Attention: Antoinette Paone, MS, MBA
Director, Regulatory Affairs CMC
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Paone:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VX-950 (telaprevir) 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.

Overall:

1. A complete description of the commercial scale drug substance and drug product manufacturing processes is required and should include process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section S.2.2 (drug substance) and P.3.3 (drug product) of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

Drug Substance:

2. Address the following regarding your starting materials:
 - a. Provide a brief description of how [REDACTED] (b) (4)
 - b. Provide a clarification for not including a test for [REDACTED] (b) (4)

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as B4 (CCI/TS) immediately
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Biopharmaceutics:

23. If available, provide information on the effect of [REDACTED] ^{(b) (4)} content on the systemic exposure (C_{max} and AUC, if available) of telaprevir tablets in humans.
24. If available, provide bioavailability/bioequivalence data for any of the lots of telaprevir tablets used in the construction of the design space. Include all relevant manufacturing information for all the lots tested in vivo including dissolution profiles.

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

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D.
Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

TERRANCE W OCHELTRIE
11/08/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 71,832

MEETING MINUTES

Vertex Pharmaceuticals, Incorporated
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
130 Waverly Street
Cambridge, MA 02139-4242

Dear Dr. Weet:

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

We also refer to the meeting between representatives of your firm and the FDA on September 28, 2010. The purpose of the meeting was to discuss topics related to the Phase 3 studies, the format and content of the safety and efficacy summaries, and the timing and content of a safety update if the telaprevir NDA is granted priority review.

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

If you have any questions, call Myung-Joo Patricia Hong at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: MEETING MINUTES



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B Meeting
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: September 28, 2010 between 2:30 – 4:00 pm
Meeting Location: White Oak Building 22, Room 2205

Application Number: IND 71,832
Product Name: Telaprevir
Indication: Treatment of chronic hepatitis C virus infection
Sponsor/Applicant Name: Vertex Pharmaceuticals, Inc.

Meeting Chair and Recorder: Myung-Joo Patricia Hong, M.S.

FDA ATTENDEES

Office of Antiviral Products

Edward Cox, M.D., Office Director,
David Roeder, Consumer Safety Officer
Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Linda Lewis, M.D., Clinical Team Leader, Division of Antiviral Products
Kendall Marcus, M.D., Deputy Safety Director, Division of Antiviral Products
Jules O'Rear, Ph.D., Virology Team Leader, Division of Antiviral Products,
Hanan Ghanous, Ph.D., DBAT, Nonclinical Team Leader, Division of Antiviral Products
Russell Fleischer, PA-C, MPH, Medical Reviewer, Division of Antiviral Products
Mark Powley, Ph.D., Nonclinical Reviewer, Division of Antiviral Products
Lisa Naeger, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
Poonam Mishra, M.D., Clinical Reviewer, Regulatory Project Manager, Division of Antiviral Products
Mary Singer, M.D., Clinical Team Leader, Regulatory Project Manager, Division of Antiviral Products
Patrick Harrington, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
George Lunn, Ph.D., Chemist, Division of New Drug Quality Assessment II, ONDQA
Thomas Hammerstrom, Ph.D., Mathematical Statistician, Division of Biometrics 7
Victoria Tyson, Chief Project Management Staff, Division of Antiviral Products
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager, Division of Antiviral Products
Stacey Min, PharmD., Regulatory Project Manager, Division of Antiviral Products

Division of Scientific Investigation

Antoine El-Hage, Ph.D., Reviewer, Division of Scientific Inspection

Office of Clinical Pharmacology

Shirley Seo, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4
Shashi Amur, Ph.D., Genomics Reviewer, Office of Clinical Pharmacology
Kellie Reynold, PharmD., Division Deputy Director of Clinical Pharmacology 4
Ruben Ayala, Ph.D., Staff Fellow, Division of Clinical Pharmacology 4
Jeffrey Florian, Ph.D., Pharmacometrics Reviewer, Office of Clinical Pharmacology
Tiang Liu, Ph.D. Pharmacometrics Reviewer, Division of Clinical Pharmacology 4
Michael Pacanowski, PharmD., MPH., Genomics Acting Team Leader, Division of Clinical Pharmacology

Office of Surveillance and Epidemiology

Cathy Miller, Safety Evaluator, DMEPA
Brantley Dorch, Pharmacist, OSE

SPONSOR ATTENDEES

Peter Mueller, Ph.D., CSO and Executive Vice President, Global Research and Development
John Weet, Ph.D., Vice President, Regulatory Affairs
Chuck Miller, Associate Director, Regulatory Affairs
Robert Kauffman, M.D., Ph.D., Senior Vice President, Clinical Development and CMO
Nathalie Adda, M.D., Senior Medical Director, Clinical Development
Scott McCallister, M.D., Vice President, Clinical Development
Antonia Kolokathis, M.D., Senior Vice President, Global Medical Affairs and Patient Safety
Henry Seto, M.D., Vice President, Global Patient Safety
Priya Singhal, M.D., MPH, Senior Medical Director, Global Patient Safety
Ann Kwong, Ph.D., Vice President HCV Franchise Lead
Tara Kieffer, Ph.D., Associate Director, Clinical Virology
Abdul Sankoh, Ph.D., Senior Director Biometrics
Varun Garg, Ph.D., Senior Director, Clinical Pharmacology
Joshua Henshaw, Ph.D., Senior Pharmacometrician, Clinical Pharmacology
Elena Koudourakis, Ph.D., Vice President, Global Registration Leader
Darryl Patrick, DVM, Ph.D., Vice President, Exploratory Development
Graeme Smith, Ph.D., DABT, Associate Director, Toxicology
Carole Varanelli, Vice President, Quality Assurance
Sean McNiff, Senior Manager, Regulatory Operations
Prabu Nambiar, Ph.D., Vice President, RA-CMC
Suzanne Foy, BPharm, MRPharmS, MBA, Senior Director, Global Regulatory Lead
Gaston Picchio, Ph.D., Senior Director, Tiboc Pharmaceuticals

1.0 BACKGROUND

Vertex Pharmaceuticals, Inc. conducted two pilot clinical studies in Europe (Studies 001 and 101). Following the two pilot clinical studies and after a pre-IND interaction with the Division, IND 71832 was submitted on November, 2005. Since the development of telaprevir in the US began in 2005, there have been numerous interactions with the Division and Vertex to guide telaprevir's development. Telaprevir was granted a "Fast Track" designation on December 7, 2007 and a rolling review ensued after receiving the first unit (pre-clinical section) on June 24, 2010. The second unit (CMC section) was submitted on July 14, 2010. Vertex Pharmaceuticals plans to submit the third unit (Study 108 Clinical Report) by mid-October, 2010. The fourth unit will complete the telaprevir NDA and is scheduled for delivery by November 30, 2010.

The DAVP sent an advice/information request letter on August 12, 2010 in response to Vertex's request submitted on July 20, 2010 regarding questions about the telaprevir NDA submission.

On September 23, 2010 the Division of Antiviral Products forwarded preliminary comments to Vertex Pharmaceuticals' questions submitted in the meeting package via electronic mail. After reviewing the Division's comments, Vertex Pharmaceuticals decided to limit the discussion to Question #2 and additional comments on Questions #1, 4, and 5.

Below Vertex Pharmaceuticals' questions are presented in bold italics; the DAVP preliminary responses and the discussions, standard font.

2. DISCUSSION

2.1 REGULATORY

Question 1:

Vertex intends to request Priority Review at the time of NDA submission, based on the criteria outlined in Section 3.4. Does the Division agree that telaprevir meets the requirements for a Priority Review designation?

DAVP agrees that the telaprevir NDA will be granted a priority review.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 2:

If telaprevir is granted Priority Review, at what point in the review cycle would the FDA require submission of the safety update discussed in CFR Title 21 Part 314.50(d)(5)?

Three months from NDA submission. Please provide a list of studies from which safety data will be submitted, as well as the format for the submission.

Discussion: Vertex Pharmaceuticals plans to submit the safety data collected from June 16, 2010 thru the October 31, 2010 cut-off date based on the three ongoing clinical studies. Three ongoing trials are: 1) Study C211 (Roll-over study of control subjects from Study C216 and used alternate dosing); 2) Study C110 (Study for HIV/HCV co-infected patients); and 3) Investigator-Initiated Intrahepatic HCV Kinetic Study. There are a total of 158 patients enrolled for these studies (106 additional subjects since the NDA cut-off). The format of the safety update will be: 1) no additional pooling or SAS datasets; and 2) a summary report of severe adverse events (SAEs)/deaths for all three studies and AEs leading to discontinuation (for Studies C219 and 110). In addition, DAVP would like to have narratives for all deaths and discontinuations due to AEs, if possible. DAVP inquired about the timing of Study C211 in relation to the safety update. Vertex confirmed that Study C211 will not be included in the Safety Update as the study will not be enrolling subjects by the time of the cutoff date (October 31, 2010). DAVP acknowledged the plan. Vertex confirmed the Safety Update would be submitted by the end of Month 3 (February, 2011).

Question 3:

Vertex acknowledges that it is likely that the Antiviral Advisory Committee would be convened as part of the NDA review process. Vertex would like to work closely with the Division prior to an Antiviral Advisory Committee and would like to discuss the preparation for the Advisory Committee Meeting during the pre-NDA meeting. Can the Division comment on the likely timing of an Antiviral Advisory Committee meeting based on our currently planned 30 November 2010 NDA submission date? Can the Division comment on which other Divisions might also participate in the Antiviral Advisory Committee?

DAVP anticipates an advisory committee (AC) meeting being held approximately 4 months following NDA submission. Based on the proposed timing of the final component of the NDA being submitted in late November-early December, an AC would likely occur in April, 2011. During our review, it is possible that DAVP will consult other divisions, such as CardioRenal (QT prolongation) and Dermatology (rash). However, the extent of interaction and their participation in an AC for telaprevir are unknown at this time.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

2.2 NONCLINICAL

Question 4:

Does the Division agree that the set of nonclinical studies that were submitted in NDA 201917 Sequence 0000 are sufficient to support the continued review of the NDA?

Yes, it is sufficient.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

2.3 CLINICAL

Question 5:

Study 108 showed that both the 8-week and 12-week telaprevir regimens were significantly superior to the currently approved treatment. Primary endpoint results of Study 108 are provided in Section 4.3.1, and a summary of key results of Study 108 is included in Appendix 1. Vertex proposes that the 12-week telaprevir regimen be the primary recommended regimen, based on its better benefit:risk profile than the 8-week regimen in Study 108.

(b) (4) *Does the Division agree with this assessment of the 8-week and 12-week telaprevir treatment durations?*

DAVP agrees that the addition of 8 or 12 weeks of telaprevir to 24 weeks of Peg-IFN/RBV substantially and likely significantly increases SVR rates among treatment-naïve subjects compared to the current standard-of-care. Further, we agree that, based on the data in the backgrounder, the 12 week telaprevir regimen appears to provide better virologic failure, relapse and SVR rates.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 6:

Study 111 showed that the 24-week response-guided treatment with telaprevir was non-inferior to the 48-week response-guided treatment with telaprevir, and that the sustained viral response (SVR) rate for the Full Analysis Set (all treated subjects) was 72%. Primary endpoint results of Study 111 are provided in Section 4.3.1, and a summary of key results of Study 111 is included in Appendix 2. Does the Division agree that Study 111 provides corroborating evidence of the efficacy of telaprevir in treatment naïve subjects, and that the results of Study 111 support the use of the response-guided treatment duration that was evaluated in Studies 108 and 111 (24 weeks of Peg-

IFN/RBV treatment for subjects who achieve an extended viral response [eRVR], defined as undetectable HCV RNA at Weeks 4 and 12; 48 weeks of Peg-IFN/RBV treatment for subjects who do not achieve an eRVR)?

The results of Study 111 appear to support Study 108 and the efficacy of telaprevir in treatment-naïve subjects. Further, the data strongly suggest that subjects who achieved an eRVR should be able to be successfully treated with a 24 week regimen, as there appears to be no added benefit for 24 additional weeks of Peg-IFN/RBV in eRVR+ subjects.

We did note that the difference between SVR rates for eRVR-(48) subjects was ~9%: 64% in Study 111 vs. 55% in Study 108. Please attempt to identify the reasons for this apparent difference in your integrated summary.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 7:

Study C216 showed that both 12-week telaprevir regimens (simultaneous start and delayed start of telaprevir) were significantly superior to standard of care for all populations of treatment-failure subjects evaluated: prior relapsers and prior non-responders, including prior null responders and prior partial responders. Primary endpoint results of Study C216 are provided in Section 4.3.1, and a summary of key results of Study C216 is included in Appendix 3.

- a. ***Vertex believes that there is no additional benefit to including a delayed start of telaprevir in the treatment regimen. Does the Division agree?***

In general, DAVP agrees, pending full review of the data.

- b. ***Vertex believes that the results of Study C216 show that the telaprevir regimens have a favorable benefit:risk across all populations of treatment-failure subjects, including prior null responders. This study was prospectively designed with a definition of prior null responders, as agreed with the Division (subjects with a $<2\text{-log}_{10}$ decrease in HCV RNA at Week 12 of previous therapy; see 27 August 2009 fax communication regarding Study C216 design). Does the Division agree with this assessment of benefit:risk?***

Based on the results contained in the meeting backgrounder, it appears that the addition of 12 weeks of telaprevir to 48 weeks of Peg-IFN/RBV substantially increased SVR rates for all populations of treatment experienced studied. However, DAVP is not able to fully agree with your assessment of benefit/risk at this time because all the data from the three experienced population trials (Study 106, 107 and C216) has not been submitted.

c. *Based on the rationale provided below, Vertex believes it is appropriate to consider response-guided treatment for prior relapsers, using the same response criteria as for treatment-naïve subjects (24 weeks of Peg-IFN/RBV treatment for subjects who achieve an eRVR; 48 weeks of Peg-IFN/RBV treatment for subjects who do not achieve an eRVR):*

- *In Study C216, the SVR rate was 83% in prior relapsers who were treated with telaprevir for 12 weeks in combination with Peg-IFN/RBV for 48 weeks (regimen without delayed start); among the prior relapsers in this treatment group who achieved an eRVR, the SVR rate was 96%.*
- *In Study 106, the SVR rate was 69% in prior relapsers treated with telaprevir for 12 weeks in combination with Peg-IFN/RBV for 24 weeks; among the prior relapsers in this treatment group who achieved an eRVR, the SVR rate was 89%.*
- *In Study 107, the SVR rate was 96% in prior relapsers treated with telaprevir for 12 weeks in combination with Peg-IFN/RBV for 24 weeks; among the prior relapsers in this treatment group who achieved an eRVR, the SVR rate was 100%.*
- *In Study 108, the SVR rate was 75% in treatment-naïve subjects treated with telaprevir for 12 weeks in combination with Peg-IFN/RBV for 24 or 48 weeks; among subjects in this treatment group who achieved an eRVR and were assigned to a Peg-IFN/RBV treatment duration of 24 weeks, the SVR rate was 89%.*

Does the Division agree that these results—SVR rates in prior relapsers that are comparable to or higher than those in treatment-naïve subjects and SVR rates of at least 90% in prior relapsers who achieve an eRVR—combined with the lack of additional benefit of a 48-week regimen compared to a 24-week regimen in treatment-naïve subjects who achieved an eRVR (as demonstrated in Study 111), are sufficient to support a response-guided regimen in prior relapsers?

We agree that the cross-study results comparing RGT SVR rates among prior relapsers and naïve subjects are very high. However, Study C216 was not designed to evaluate RGT in any subgroup, and there are differences in response rates for this population noted in Studies 106 and 107. As such, this proposal will be a review issue. Please provide in the NDA your rationale with supporting data.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 8:

Vertex is seeking the following indication in this original NDA: Telaprevir, in

combination with peginterferon-alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease including both patients who are treatment naïve and those who have been treated previously with interferon-alfa alone or in combination with ribavirin, including prior null responders, partial responders, and relapsers. Does the Division agree that the data in pivotal studies 108 and C216 and supportive study 111 are sufficient to support the indication being sought?

Discussion of the proposed labeling is premature at this time; the final wording will be based on our completed NDA review.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 9:

Does the Division agree with the proposal for meeting the requirement for an Integrated Summary of Efficacy (ISE) as described in Section 4.3.7 and the proposal for meeting the requirement for an Integrated Summary of Safety (ISS) as described in Section 4.4.3?

DAVP agrees.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 10:

Vertex is planning to write a single Summary of Clinical Efficacy (SCE) that includes data from the treatment-naïve and treatment-failure populations because these data are supportive of the overall efficacy of telaprevir and the proposed indication, which includes both patient populations. A summary of the proposed content of the SCE is provided in Section 4.3.3 through 4.3.5. Does the Division agree with the format and structure of the single proposed SCE to support the indication as proposed in Question 8?

DAVP agrees.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 11:

With reference to Section 4.4, does the Division agree with the proposed format and treatment arms and study pooling strategies in the Summary of Clinical Safety, as described in Section 4.4.1 and in the ISS Statistical Analysis Plan (IND 71,832/Seq 0480)?

DAVP agrees.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 12:

A table of all clinical pharmacology studies that will be included in the NDA was included in Section 5 of the Request for Comment: NDA Questions (IND 71,832/Seq 0472). Results of the studies are summarized in Sections 4.1 and 4.2, and have been incorporated into the draft US package insert in Appendix 7. Plans for a pooled population pharmacokinetic analysis are provided in Section 4.2.3. Does the Division agree that the set of clinical pharmacology studies and the pooled population pharmacokinetic analysis are sufficient to support registration?

Yes, the set of clinical pharmacology studies conducted to date and the population pharmacokinetic analysis plan appear sufficient to support your NDA submission. We recommend that you also perform exposure-response analyses for efficacy (e.g., SVR) and safety (e.g., rash events) based on derived PK parameters (e.g., C_{trough} , $C_{avg,ss}$, AUC_{ss}). These analyses should be included in your NDA submission.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 13:

Given the Division's response to Question 1 (regarding covered studies) in the Request for Comment: NDA Questions (IND 71,832/Seq 0472), Vertex would like to clarify the regulatory intent of Study C208 in the context of the pre-NDA meeting. The regulatory intent of Study C208 is to support approval for the use of either PegIntron/Rebetol or Pegasys/Copegus with telaprevir. Does the Division agree? (b) (4)

(b) (4)

Given the importance of dosing telaprevir with food, (b) (4), Vertex proposes a dosing schedule of 3 times daily (see draft US Package Insert in Appendix 7). Does the Division agree?

DAVP previously concluded that there are sufficient data available to support co-administration of telaprevir with either currently approved pegylated interferons (PegIntron® and Pegasys®). (b) (4)

(b) (4) Therefore, we anticipate the initial dosing interval will be q8h.

(b) (4)

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 14:

Vertex conducted 2 thorough QT/QTc studies, and reports for both studies have been submitted (Study 008: IND 71,832/Seq 0198; Study C136: IND 71,832/Seq 0476). The draft US package insert in Appendix 7 incorporates the results of these studies. Does the Division agree that these 2 thorough QT/QTc studies are sufficient to support the labeling regarding QTc?

The two QT/QTc studies appear to fulfill the requirement for an adequate QTc study, and should support the proposed labeling. We note that the results demonstrate a positive effect of telaprevir on QT prolongation. (b) (4)

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 15:

Vertex is currently preparing to write a Medication Guide for telaprevir that will cross-reference the Peg-IFN and RBV Medication Guides. Taking into consideration the extent of information currently available (prior to the NDA submission), does the Division consider that a Medication Guide is likely to be sufficient for the telaprevir REMS?

DAVP agrees that a Medication Guide will be required for telaprevir based on its safety profile (i.e., proposed WARNINGS related to rash, (b) (4), and anemia) and it seems reasonable to propose a REMS consisting of a Medication Guide. Please submit the proposed REMS and Medication Guide in your application. However, a complete review will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Question 16:

Does the Division agree with the proposal to cross-reference the Peg-IFN and RBV package inserts in the telaprevir US package insert (see draft US Package Insert in Appendix 7)?

Where appropriate cross-reference to the Peg-IFN and RBV package inserts will be acceptable. If deemed necessary for safety purposes, however, specific discussions of Peg-IFN and/or RBV may be included in a telaprevir label.

Discussion: The sponsor accepted FDA's response; no discussion occurred.

Additional Comments

1. Please refer to the "Guidance for Pharmacogenomic Data Submissions." Please include reports for pharmacogenomics analyses and the associated data with the NDA submission. Specifically, please include analyses according to IL-28B genotype for all trials, in addition to any available genotyping results for safety-related endpoints (e.g., rash).

Discussion: Please see the discussions under additional comment #4.

2. In the NDA, please request a "Deferral" for studies in pediatric subjects 3-18 years of age and a Waiver for subjects <3 years of age. A Written Request for telaprevir is being prepared and comments will be sent to you in the very near future.
3. With respect to HIV/HCV co-infected subjects, we note that Study 110 is ongoing. (b) (4)

Discussion: The sponsor accepted FDA's additional comments #2 and 3; no discussion occurred.

4. During the Pre-NDA meeting, please provide a brief update on the following pre-clinical and clinical efforts being carried out to determine:
 - a. the impact of IL-28B genotype on the responses observed in the Phase 3 trials.

Discussion (additional comment # 1 and 4a): Vertex Pharmaceuticals will provide the IL-28B data based on a Phase 3 study report (a stand alone Study C216-28B) which includes 536 patients enrolled in the initial NDA. Vertex has collected samples from approximately 527 subjects to perform genomic testing. Vertex stated that de-identification is required so IL-28B genotype will not be in the virology datasets. From Study 108 (pivotal Phase 3 study for naïve patients) and Study 106 (Phase 2 study for non-responder), there are samples from approximately up to 800 patients to be tested. IL-28B genotyping analysis is ongoing using de-identified samples retrieved from US sites of Studies 108, 106,

and 104. These reports retain some demographic characteristics but Vertex will not be able to submit the data with the NDA submission and proposed to submit analyses once they become available (i.e., by the end-of-year). DAVP (Genomics Group) acknowledged that the de-identified data would be in a stand alone report for C216. DAVP also agreed that the Studies 104, 106, and 108 reports may only be available after the submission by the end of the year. DAVP questioned whether ethnicity/race data were included in the analyses. Vertex stated that these variables were not retained in Studies 104, 106, and 108 due to the need to de-identify. DAVP also asked whether Vertex has preliminary data on interferon stimulating gene expression either in Study C216 or C211. Vertex responded that the data from C211 will be collected first and will provide clarity regarding which interferon stimulating genes may be studied from Study C216 or C211 at a later time. DAVP and Vertex will have a follow-up discussion after this meeting to clarify the parameters. Vertex will also provide more details of the information retained in the de-identification process for the samples from Studies 108, 106, and 104.

- b. the etiology and mechanism of rash.

Discussion (additional comment # 1 and 4b): Vertex instituted the updated Phase 3 rash assessment and management plan which includes intensive data collection (e.g., photographs, biopsies, dermatology consult) for rashes (Grade 3, SAE, D/Cs). The management plan includes: 1) Dermatology expert panel (DEP) will be consulted for adjudication and evaluation of the cases and the report will be included in Module 5 of the NDA submission; 2) a comprehensive rash analysis utilizing rash Special Search Category (SSC) will be included in the Summary of Clinical Safety (M2.7.4); 3) *in vitro* and *in vitro* metabolite characterization; and 4) pharmacogenomic studies (HLA typing, Pgp polymorphism). Vertex has performed blinded assays and will provide details of the overall results in the IND.

Vertex described findings from the DEP (i.e., eczematous-like rash, spongiotic dermatitis histopathology). DAVP asked whether there was any HLA evaluation. Vertex responded that there was no association with the 121 alleles tested in a pilot study; a larger study is ongoing; but it does not appear to be abacavir-like. DAVP mentioned the DRESS case report that has been recently published (Montaudié H, Passeron T, Cardot-Leccia N, Sebbag N, Lacour JP. Drug Rash with Eosinophilia and Systemic Symptoms due to Telaprevir. *Dermatology*. 2010 Aug 25). Vertex stated that this was a Study 107 case, which was previously submitted to the IND as a safety report. The published case report was written by the dermatologist at the site in France without knowledge or consent from the local investigator. The DEP had already examined the case and conservatively indicated it had DRESS-like features and the case had been previously reported as an IND safety report. Vertex had updated the investigator's brochure (IB) to include DRESS in the Summary of Guidance to Investigators section in 2009 to properly communicate

with the investigators. DAVP asked whether Vertex was looking at a genome wide assessment study (GWAS) study. Vertex stated no plans at this time. DAVP asked about exposure/response. Vertex responded that Study 104 and 104EU demonstrated a weak association but this was not confirmed in study 106 and the Phase 3 studies.

- c. the etiology and mechanism of the ano-rectal toxicities.

Discussion (additional comment # 1 and 4c): Vertex provided the following explanations in regards to the etiology and mechanism of the ano-rectal toxicities:

- The symptom was very complex to explain. Study 104 has been reported under various terms such as hemorrhoids, anal pruritis, or ano-rectal discomfort. Virtually all have been found to be mild to moderate.
- There was no relationship to generalized pruritis or rash.
- A special search category has been created to summarize incidence and will be reported in the Summary of Clinical Safety (M2.7.4).
- Vertex tested telaprevir metabolites with no findings in the colon or rectum in a toxicity study. Information regarding metabolites and dermal irritation potential will be included in the NDA and discussed in relevant summaries.

DAVP asked whether there was any pattern associated with this disorder and about the timing of resolution of the adverse reaction. Vertex responded that onset was often within the first two weeks, but also happened at later times. Vertex added that the time to resolution seemed to be within 4 to 8 weeks. Most cases were not severe and were not associated with discontinuation. The discontinuation of treatment due to rectal issues was less than 1%. DAVP stated that people will want to know about it since it may cause people to discontinue the drug. DAVP stated that Vertex should come up with a management plan at some point in preparation for an AC meeting but it does not need to be in time for the NDA submission.

5. Please see the attached two documents for site inspection materials (Appendix A and B). The Division of Scientific Investigation (DSI) requests two types of data to be submitted to the NDA: 1) data to address the clinical data submitted in the NDA that will be used for inspection background materials (Item I and II); and 2) data to address the site selection process (Item III). The submission of these materials is voluntary and is not required by DSI.

Discussion: Vertex is working on the site inspection background materials as described in Appendix A. Vertex proposed to include it in Module 5 of the NDA. For the datasets outlined in Appendix B, Vertex SAS programmers and clinical operations are assessing

the timeline required to fulfill this request. Vertex requested to have the opportunity to schedule teleconferences with DSI for specific clarification as Vertex develops the Appendix B request. DSI reiterated that the program is voluntary and Vertex should not let it get in the way of submitting the NDA. (Appendices A and B were sent with DAVP's preliminary comments)

3.0 ACTION ITEMS

- Vertex will provide more details of information retained in the de-identification process for the samples from Studies 108, 106, and 104.
- Vertex will provide clarification regarding what interferon stimulating genes may be studied at a later time from Study C216 or C211.
- Vertex needs to provide information discussing the interaction with contraceptives and how they will address hormonal and non-hormonal contraceptives since no hormonal treatment was recommended with ribavirin.
- Vertex will submit the abstracts for AASLD meeting to the file as a general correspondence.
 - Vertex submitted the abstracts to the file on October 4, 2010.
- DAVP and DSI will work on a simpler template for the datasets.
- DSI indicated that Vertex should make a statement in the NDA submission regarding no terminations of sites due to GCP non-compliance.

Other comments provided during the meeting

- The MG-only REMS will be required. [REDACTED] (b) (4). DAVP will work with Vertex to finalize the REMS after reviewing the proposed label.
- DAVP recommends Vertex consult a patient-friendly language consulting group for the MG, and for other important issues patients need to know. FDA recommends using language at the 6-8 grade level.
- The labeling review will start late in the review cycle.
- The most likely topics for the AC include: efficacy, resistance, rash, ano-rectal signs and symptoms, and anemia.
- Vertex needs to prepare for an AC meeting in regards to topics related to: 1) effectiveness of the drug; 2) management of toxicities; 3) drug-drug interactions; 4) specific populations

(i.e., pediatrics, HIV/HCV co-infected patients); and 5) treatment in advanced liver disease.

- Pediatric written request (WR) is almost ready and will be sent to Vertex.
- Vertex needs to submit a trade name for review.

4.0 ATTACHMENTS AND HANDOUTS

Two slides attached below were presented by Vertex Pharmaceuticals to introduce their clinical development program.





(b) (4)

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

/s/

DEBRA B BIRNKRANT
10/22/2010

Reference ID: 2853666

Reference ID: 2952374



NDA 201-917

NDA PRESUBMISSION ACKNOWLEDGEMENT

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

Dear Dr. Weet:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: TELAPREVIR
TABLET, 375 mg

Date of Submission: JUNE 24, 2010

Date of Receipt: JUNE 24, 2010

Our Reference Number: NDA 201-917

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning 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 Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Myung-Joo Patricia Hong, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

MYUNG-JOO PATRICIA HONG, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201917	ORIG-1	VERTEX PHARMACEUTICA LS INC	TELAPREVIR

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

/s/

MYUNG JOO P HONG
07/21/2010

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

1. APPLICANT'S NAME AND ADDRESS

VERTEX PHARMACEUTICALS INCORPORATED
Chuck Miller
130 Wavery Street
Cambridge MA 02139-4242
US

**4. BLA SUBMISSION TRACKING NUMBER
(STN) / NDA NUMBER**

201-917

2. TELEPHONE NUMBER

617-444-6207

**5. DOES THIS APPLICATION REQUIRE
CLINICAL DATA FOR APPROVAL?**

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

TELAPREVIR

6. USER FEE I.D. NUMBER

PD3010502

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

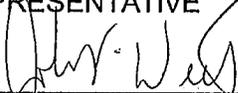
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Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive,
Room 3046
Rockville, MD 20852-1448

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12420 Parklawn Drive,
Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	VP Regulatory Affairs	21 June 2010

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$1,405,500.00

Form FDA 3397 (03/07)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Vertex Pharmaceuticals Incorporated
Attention: Prabu Nambiar, Ph.D., MBA, RAC
Vice President, Regulatory Affairs
130 Waverly Street
Cambridge, MA 02139

Dear Dr. Nambiar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-950.

We also refer to the meeting between representatives of your firm and the FDA on March 19, 2008. The purpose of the meeting was to discuss Chemistry, Manufacturing and Controls (CMC) topics for VX-950, including stability planning, specifications, and design space/quality by design proposals for drug substance and drug product.

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

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Vertex Pharmaceuticals Incorporated
Application Number:	IND 71,832
Product Name:	VX-950 Tablets; (b)(4) 375 mg
Meeting Requestor:	Jennifer Jackson, Ph.D., Vice President Regulatory Affairs, Vertex Pharmaceuticals Incorporated
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC) End of Phase 2 (EOP 2) Meeting
Meeting Date and Time:	Wednesday, March 19, 2008 1400 – 1500 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	February 15, 2008
Meeting Chair:	Elaine Morefield, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment:Division of Pre-Marketing Assessment II

Elaine Morefield, PhD, Division Director (15 September 2008)

Stephen Miller, PhD, Pharmaceutical Assessment Lead (15 September 2008)

Division of Pre-Marketing Assessment III & Manufacturing Science

Christine Moore, PhD, Branch Chief, DPMA III & MS (23 September 2008)

Sharmista Chatterjee, PhD, Review Chemist (15 September 2008)

Division of Pre-Marketing Assessment I

Scott N. Goldie, PhD, Regulatory Health Project Manager for Quality

Division of Anti Viral Products

Carrie M Ceresa, Regulatory Health Project Manager (15 September 2008)

Anita Bigger, Reviewing Pharmacologist and Acting Team Leader (22 September 2008)

VERTEX ATTENDEES:

Patricia Hurter, Vice President, Pharmaceutical Development

Pierre Boulas, Director, Analytical Development

Craig Dunbar, Senior Director, Formulation Development

Eda Montgomery, Senior Director, Commercial Support and Lifecycle Management

Minzhang Chen, Director, Technical Operations - Drug Substance

Thomas Gandek, Director, Technical Operations - Drug Product

Pat Connelly, Senior Director, Materials Discovery and Characterization

Jennifer Jackson, Vice President, Regulatory Affairs

Mark De Rosch, Senior Director, Regulatory Affairs

Antoinette Paone, Associate Director, Regulatory Affairs

John Condon, Vice President, Pharmaceutical Operations

Luc Janssens, Senior Director, Regulatory CMC, Tibotec BVBA

Nico Niemeijer, Senior Director, ChemPharm Team Leader, Tibotec BVBA

1.0 BACKGROUND

Vertex Pharmaceuticals, Inc., (Vertex) is developing VX-950, proposed for the treatment of chronic hepatitis C infection. Vertex requested a Chemistry, Manufacturing and Controls (CMC) type B End of Phase 2 meeting on January 30, 2008, to discuss stability planning, specifications, and design space/quality-by-design (QbD) proposals for the manufacture of VX-950 drug substance and drug product. The face to face meeting was granted on January 2, 2008, scheduled for March 19, 2008, between 1400 - 1500 ET at the Food and Drug Administration White Oak Campus in Silver Spring, Maryland. The corresponding briefing package that provided additional information on discussion topics and final questions was sent by Vertex on February 15, 2008, providing additional information on discussion topics and questions. The preliminary responses to the questions contained in the briefing package were archived and shared with Vertex on March 19, 2008, to promote a collaborative and successful discussion at the meeting.

2.0 DISCUSSION

2.1 Discussion Topic: Questions 1 - 2: Stability

Vertex intends to provide stability data in the NDA to support a 36-month room temperature retest interval for telaprevir drug substance (Section 3.2.S.7.2) and a 24-month room temperature shelf life for drug product (Section 3.2.P.8.2.2). The (b) (4) is manufactured at a separate facility than the tablets, and Thus, Vertex handles the (b) (4) (b) (4) with its own release and stability specification, storage condition, shelf life, shipping condition, etc. Stability data will be provided in the NDA to support (b) (4) (b) (4) (Section 3.2.P.8.2.1)

The intended approach at the time of NDA submission of a maximum 24-month shelf life for drug product, (b) (4) is supported by the "End-to-End" stability plan (Section 3.2.P.8.1.2).

- 2.1.1 Briefing Package Question 1. Does the Agency agree that the formal (Registration) stability protocols for drug substance (b) (4) and drug product support the intended retest interval/shelf life at the intended storage condition, presuming that the stability data collected support the intended shelf life and storage condition?

FDA Preliminary Response: We will follow the ICH approach for extrapolation beyond real-time data. Will any supportive data beyond (b) (4) be available on API?

Meeting Discussion: Vertex acknowledged receipt of FDA's preliminary response and indicated that there would be supportive data beyond (b) (4) available on the API. No further discussion occurred during the meeting.

2.1.2 Briefing Package Question 2. Does the Agency agree that telaprevir (b) (4) can be handled as a separate material from drug product with its own expiration date and that the date of manufacture for the tablets will be based on the date when (b) (4)?

FDA Preliminary Response. We agree that the (b) (4) will be handled as a separate material with its own expiration dating period, and that the tablet expiration dating period (b) (4). The justification for the (b) (4) expiration dating period would be strengthened by clarification of whether Vertex will verify (b) (4) prior to use.

2.2 Discussion Topic Questions 3 - 4: Specifications

Critical quality attributes of telaprevir drug product (Section 3.2.P.2.1, Table P.2.1-2) have been designated based on the target product profile (Section 3.2.P.2.1, Table P.2.1-1). Stability results (Section 3.2.P.8.1.1) coupled with modeling and regression analysis (Section 3.2.P.8.1.3) have demonstrated that, (b) (4)





(b) (4)

2.2.1 Briefing Package Question 3. Does the Agency agree that the proposed specifications for a) telaprevir tablets, b) [redacted] (b) (4) and c) drug substance support commercialization of telaprevir?

FDA Preliminary Response: The proposed specifications have been based on the significant amount of knowledge accumulated to date, and appear to support commercialization. At the time of NDA submission, additional information will be available and the acceptance criteria as well as the attributes measured will be assessed as part of the NDA review. Given the importance of maintaining the [redacted] (b) (4) [redacted] to the Target Product Profile, we would like to discuss the following at the EOP-2 meeting:

A. Does your current knowledge allow you to [redacted] (b) (4) [redacted] ?

D. Regarding the overall control strategy for API, please provide in the NDA additional justification for having no specification for the (b) (4).

Meeting Discussion: Vertex and FDA referred to slides 2 through 4 to facilitate discussion of the physical stability attributes and specifications. FDA acknowledged Vertex's presentation and noted it would be included in the meeting minutes. FDA recommended that Vertex include the data they referred to in their presentation in the pharmaceutical development package of the NDA along with any additional data as scientific justification to support their findings. FDA indicated that the concurrence with Vertex's findings would be a data driven review issue based on the NDA submission.

2.2.2 Briefing Package Question 4. Does the Agency agree that the stereochemical control strategy is appropriate to support commercialization of telaprevir?

FDA Preliminary Response: Yes, with a few questions:

(b) (4)

C. Please comment on the applicability of the ICH Q6A recommendation relating to identity testing for single enantiomer drug substances.

Meeting Discussion: Vertex referred to slide 5 to facilitate the discussion. FDA indicated that the approach appears reasonable, but the applicability of the stereochemical control strategy is a review issue based on the scientific justification included in the pharmaceutical development report of the NDA. FDA recommended that Vertex include any additional data, references, and explanations regarding the expiration and stability with the original submission of the NDA.

2.3 Discussion Topic: Questions 5-6: Manufacturing:

Vertex plans to register 2 manufacturing sites for (b) (4) which may be used interchangeably. For routine commercial operation, 1 supply chain will be managed by Vertex (b) (4) and the other will be managed by our European corporate partner, Janssen (b) (4). The interchangeable material from either supply chain to manufacture commercial drug product for the US market will be supported in the NDA as described for drug substance in Section 3.2.S.2.1, and for (b) (4) drug product in Section 3.2.P.3.1.

The (b) (4) will be validated for commercial supply. The proposal to validate (b) (4) is provided in Section 3.2.P.3.1.1 and the process for implementation of these changes is provided in the CMC Regulatory Agreement.

- 2.3.1 Briefing Package Question 5: Provided that DS (b) (4) DP CQA's meet their acceptance criteria, does the Agency agree that material from the Vertex and Janssen supply chains are interchangeable?

FDA Preliminary Response: It would be acceptable to interchange material from the two sites, if sufficient evidence is provided to assure that products from these two sites are of acceptable quality. This would comprise, for example, demonstrating adequate in-process controls in conjunction with meeting of end product acceptance criteria. It is recommended to include in the NDA comparative data for (b) (4) made at the two sites.

Additional follow up questions:

- It is noted that (b) (4) would be manufactured using different equipment at the two sites. Would the design space provided for (b) (4) be applicable to both these processes?

Meeting Discussion: Vertex acknowledged receipt of FDA's preliminary response. Vertex committed to update their model to allow for dependence of coefficients on equipment type where appropriate and supply sufficient scientific justification to support their design space in their NDA.

Vertex intends to qualify a rework procedure for (b) (4) (Section 3.2.P.2.3.3.1-Rework). A series of investigations is currently being completed to determine whether (b) (4) which does not meet the acceptance criteria for particle size, bulk density, and/or physical form can be reworked by (b) (4)

(b) (4)s. The goal of the qualification studies is to demonstrate that the (b) (4)

2.3.2 Briefing Package Question 6: Does the Agency agree with the proposal to qualify the rework procedure for (b) (4) to be specified in the NDA?

FDA Preliminary Response. We need more information on the following points:

A. We would like to understand the situations where you might use the reworking process. Is this to be used (b) (4) that has gone out of specification on storage?

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the administrative file. No further discussion occurred during the meeting.

B. Will stability data on the (b) (4) with two cycles of reworking be available at NDA submission?

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the administrative file. No further discussion occurred during the meeting.

C. Regarding the Comparability Protocol (page 295), will you continue stability studies of first commercial tablets made with reworked (b) (4) beyond 3-mo? Will this include direct measurement of (b) (4) as in the formal stability protocol (page 436)? If dissolution were to be used to assess comparability of (b) (4), what f2 value would be needed to show (b) (4)?

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the administrative file. Vertex indicated that stability studies of commercial tablets will be continued beyond three months with reworked (b) (4). Vertex also indicated that direct measurement of (b) (4) would be a part of the formal stability protocol. Vertex indicated that the f2 value would be submitted in the form of a written response. No further discussion occurred during the meeting.

2.4 Discussion Topic Question 7: Excipient Qualification

The proposed levels of hypromellose acetate succinate (HPMCAS, Section 3.2.P.2.1.2.1) and sodium stearyl fumarate (SSF, Section 3.2.P.2.1.2.2) were chosen by Quality-by-Design. Both HPMCAS and SSF are listed in the FDA Inactive Ingredients Database/GRAS list and are in FDA-approved products. Vertex believes that the use of these excipients is justified based on the observed benefit to the product. Moreover, HPMCAS was used in all toxicology studies at a level high enough to justify the commercial dose. Furthermore, Vertex believes that, while the level of SSF is higher than the FDA database (b) (4), this increase is unlikely to present a safety risk and is, therefore, justified.

2.4.1 Briefing Package Question 7: Does the Agency agree with our assessment that the excipients are qualified?

FDA Preliminary Response. The excipients appear to be qualified. However, we are waiting for additional information from you in order to complete our assessment.

Meeting Discussion: Vertex acknowledged receipt of FDA's preliminary response and additional information would be submitted to the administrative file. No further discussion occurred during the meeting.

2.5 Discussion Topic Questions 8-9: Design Space

We have presented a substantial amount of data in the package on our proposed design space for drug substance (Section 3.2.S.2.6) and drug product (Section 3.2.P.2.3.3, Section 3.2.P.2.4). We do not ask and we do not expect the ONDQA reviewers to scientifically evaluate and comment on the specific design space data presented in their entirety. Rather, we are seeking general input from ONDQA on our overall approach to Quality-by-Design, including connection of the target product profile to critical quality attributes, critical process parameters, control strategy, process validation, quality systems, and flexible regulatory approaches. Amongst the process development data provided, are detailed demonstrations of the design space for the (b) (4)

processes.

- 2.5.1 Briefing Package Question 8: Overall, is the Agency satisfied with level of detail and scientific explanation defining the design space for drug substance, (b) (4) and drug product?

FDA Preliminary Response. The level of detail regarding data collection for the design space appears to be sufficient. It is suggested to include the rationale for determination of key and critical process parameters together with the discussion of criticality. It is also recommended to include a discussion about the criticality of interaction of parameters, including the non critical parameters. It is noted that regression models were used to define PAR for design space. For such cases it is recommended to include plans for model verification and update for continual improvement and the limits for equation validity.

Meeting Discussion: Vertex referred to slide 6 to facilitate the discussion. FDA and Vertex discussed the data required to support the discussion of criticality of drug product process parameters and parallels with the drug substance critical process parameter determination, and recommended ways to present these data in the NDA.

Additional questions pertaining to design space development:

- A. How was the effect of scale built in determination of design space?

Meeting Discussion: Vertex referred to slide 6 to facilitate the discussion. Vertex committed to provide the information to support the scale factor in design space development in the NDA.

B. The use of FEA and mass transfer models to design blister tooling and container closure system respectively, is recognized as a valid science based approach. In order to get a better understanding of these models it is recommended to provide more details in the final submission (e.g. model assumptions, approach, model verification and model prediction)

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the NDA. No further discussion occurred during the meeting.

C. It is noted that the description of the processes (P2.5 and P.3) include only ranges on critical and key parameters in terms of PAR. In some cases, successful operation of the process is further constrained within the PAR, based upon equations. We recommend including in the summary tables (e.g. Table P.3-8) an explanation of how the additional constraints imposed by the equations would be implemented.

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the administrative file. No further discussion occurred during the meeting.

D. Providing, in the final submission, an example of current manufacturing practice (e.g. an executed batch record) for both the drug substance, as well as the drug product, would be helpful in facilitating our overall understanding.

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the administrative file. No further discussion occurred during the meeting.

The proposed registered (b)(4) process in Section 3.2.P.3.3 includes PARs for critical and key process parameters and in-process controls, including equations, when needed. We have demonstrated that provided the (b)(4) CQA acceptance criteria are met, the (b)(4) process is robust and produces drug product that meets its CQAs. (b)(4) equipment with modified design, or, for example, (b)(4) NORs or PARs to produce the same (b)(4) CQAs.

2.5.2 Briefing Package Question 9: Would the Agency consider an alternate definition of the design space for (b)(4) as achieving the critical quality attributes of the (b)(4); (b)(4) i.e., rather than registering critical and key process parameters and in-process controls, only critical quality attributes of the (b)(4)? In this case any combination of process parameters, (b)(4) etc. could be implemented under flexible regulatory approaches provided the (b)(4) meets the desired acceptance criteria.

FDA Preliminary Response. Describing the design space as the output attributes alone is not consistent with the Q8 definition of design space. There is a potential for process parameters to interact in a way not previously anticipated and possibly not detected in the intermediate quality. A comparability protocol could be an alternative approach to down-regulate post-approval changes for process modifications.

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response. No further discussion occurred during the meeting.

2.6 Discussion Topic Questions 10-12: CMC Regulatory Agreement

The proposed CMC Regulatory Agreement consists of designated manufacturing sites, process descriptions (based on QbD and process understanding), control strategy, shelf life/retest interval, storage condition, container closure system, post-approval stability commitment, quality systems/change management, flexible regulatory approaches, and comparability protocol(s) (if any intended for the NDA). The control strategy has been developed which considers all control points from drug substance starting material specifications through drug product container closure system and storage condition. The flexible regulatory approaches describe our understanding of the regulatory submission needed for each type of change to process, material, or specifications, along with the process to be used to implement the changes (including the regulatory submission needed). Specific examples of such changes and comparison to the current regulatory guidance is included, along with examples of changes that are anticipated to be made to the telaprevir process described in this submission, and Vertex' plans to evaluate, assess risk, and implement these changes.

2.6.1 Briefing Package Question 10: Does the Agency agree with the intended content of the CMC Regulatory Agreement and its intended location in Module 1.11.1?

2.6.2 Briefing Package Question 11: Does the Agency agree with the presentation and format of the telaprevir control strategy for drug substance (b) (4) and drug product contained in the CMC Regulatory Agreement?

2.6.3 Briefing Package Question 12: Have we sufficiently represented QbD in telaprevir such that our proposal for flexible regulatory approaches meets the Agency's expectations for information to be provided on pharmaceutical development, quality systems, risk management, change control, and product lifecycle management, and such that our proposed framework for telaprevir is reasonable? We are hoping to discuss the specific examples of our proposed flexible regulatory approaches during the meeting to allow us to mutually understand the expectations.

FDA Preliminary Response. At the present time, there are active discussions taking place within FDA to identify the best path forward for implementing a Postapproval Management Plan or PMP. Until this issue is resolved, we can not provide feedback on your PMP proposal for telaprevir. If you include a PMP in the NDA, we may not be able to review it; and our acceptance of the PMP proposal may not be part of the approval of the NDA, until FDA has publicly announced its readiness to accept such a proposal. If FDA's announcement is made before your NDA is submitted, we will be happy to provide comments on these three questions.

You may also wish to consider whether Comparability Protocols might provide an approach to reducing reporting requirements.

Meeting Discussion: Vertex referred to slide 7 to facilitate the discussion. Vertex and FDA discussed the types of manufacturing changes that potentially could be made under a Postapproval Management Plan (PMP) or made under comparability protocols. Vertex and FDA also discussed the pathway for submission of these comparability protocols, and FDA committed to review the proposed comparability protocols but not the data prior to the NDA submission in a risk based assessment.

2.7 Discussion Topic Question 13: Organization of Information in CTD

Using Quality-by-Design (ICH Q8 and Q9), Vertex has demonstrated our design space(s) for drug substance (Section 3.2.S.2.6), (b)(4) (Section 3.2.P.2.3.3.1), and tablets (Section 3.2.P.2.3.3.2). Using the critical and key process parameters from the design space, we have described controls of critical process steps in Section 3.2.S.2.4 for drug substance and in Section 3.2.P.3.4 for (b)(4) and tablets. In the NDA submission, the information will be organized and presented as outlined in this meeting information package. Therefore, our descriptions of processes and the development of our design space (with normal operating ranges and proven acceptable ranges) will be contained in Module 3, while the regulatory process descriptions (with proven acceptable ranges for critical and key parameters) will be presented in the CMC Regulatory Agreement.

As the (b)(4) is an (b)(4) with its own release and stability specification, storage condition, shelf life, shipping condition, etc., we intend to organize the (b)(4) information in Module 3.2.P by including as examples: 1) the process description for the (b)(4) in

Section 3.2.P.3.1.1 and the process description for tablets in Section 3.2.P.3.1.2 and 2) the specification for the (b)(4) in Section 3.2.P.5.1.1 with the specification for the tablets in Section 3.2.P.5.1.2.

- 2.7.1 Briefing Package Question 13. Does the Agency agree with the proposed organization of CMC information in the CTD, including the locations for the product development data, regulatory commitments, and proposed flexible regulatory approaches?

FDA Preliminary Response: We agree with the organization/location of the product development data and regulatory commitments.

Note that although the CTD-Q¹ and the eCTD² specification imply that separate drug substance sections should be submitted for each different manufacturer, you should provide some means to facilitate comparison of manufacture at the two sites. This might be, for example, by providing tabular comparisons, or by providing a single eCTD manufacturing section with the XML attribute manufacturer= [REDACTED] (b) (4).

Meeting Discussion: Vertex acknowledged receipt of and agreed with FDA's Preliminary Response, and committed to respond in writing to the administrative file or to revisit this subject at the preNDA meeting. No further discussion regarding this topic occurred during the meeting.

At this meeting, FDA concurred with Vertex's proposal (as described in the February 19, 2008, submission; SDN-191/Ser 0191) for transitioning from the current uncoated, capsule-shaped tablet (to be used in Phase 3 clinical studies) to a film-coated, capsule-shaped tablet of the same formulation (for commercial distribution).

3.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA Questions for Discussion at EOP-2 Meeting:



Meeting Discussion: Vertex referred to slide 8 to facilitate the discussion. Vertex committed to provide scientific data to address the questions posed by FDA in the NDA.

¹ http://www.ich.org/MediaServer.jserv?@_ID=556&@_MODE=GLB

² http://estri.ich.org/eCTD/eCTD_Specification_v3_2.pdf

4.0 ACTION ITEMS

There were no other action items other than those included in the meeting discussion entry for each question in Section 3.0.

5.0 CONCURRENCE:

{See appended electronic signature page}

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{See appended electronic signature page}

Elaine Morefield, Ph.D.
Division Director
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6.0 ATTACHMENTS AND HANDOUTS

The following slides were presented and distributed by Vertex during the meeting to facilitate discussion.

(b) (4)



Linked Applications

Sponsor Name

Drug Name

IND 71832

VERTEX PHARMS

VX-950

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

/s/

SCOTT N GOLDIE
09/23/2008

ELAINE M MOREFIELD
09/23/2008