DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201917/S-10
NDA 201917/S-12

SUPPLEMENT APPROVAL

Vertex Pharmaceuticals, Incorporated
Attention: Betsy Stone
Senior Manager, Regulatory Affairs
130 Waverly Street
Cambridge, MA 02139

Dear Ms. Stone:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received January 11, 2013 (Supplement-10) and May 9, 2013 (Supplement-12), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Incivek® (telaprevir), 375 mg tablets.

We acknowledge receipt of your amendments dated January 15, 2013, January 29, 2013, January 30, 2013, February 1, 2013, February 22, 2013, March 1, 2013, March 21, 2013, March 29, 2013, May 14, 2013, May 28, 2013, June 11, 2013, June 28, 2013, July 16, 2013, August 21, 2013, September 23, 2013, October 3, 2013, October 8, 2013, October 11, 2013, October 15, 2013, October 23, 2013, and October 25, 2013.

These "Prior Approval" supplemental new drug applications propose the following changes:

1. NDA 201917/S-10 - proposes a change in the dosage and administration of the product from 750 mg every eight hours to 1,125 mg twice daily (every 10-14 hours).

2. NDA 201917/S-12 - proposes to move the anticonvulsant medications carbamazepine, phenobarbital, and phenytoin from the Drug Interaction section (Section 7) to the Contraindication section (Section 4) of the Prescribing Information (PI). The analgesic medications alfentanil and fentanyl were added as potential drug interactions when used with telaprevir. Drug interactions with carbamazepine and phenytoin were added in Table 6 and 7 of Section 12.3.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 23, 2013, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for ages 0 to under 3 years because necessary studies are impossible or highly impracticable, very few patients aged 0 to under 3 years with Chronic Hepatitis C (CHC) require treatment, and peginterferon alfa and ribavirin cannot be used in children under 3 years of age.

We remind you of the deferred pediatric studies, PMRs 2052-1 and 2052-2, issued in our June 28, 2013 letter for NDA 201917. We deferred submission of your pediatric studies for ages 3 through 17 years of age for this application because this product was ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2052-1 Evaluate pharmacokinetics (PK) of telaprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine weight-based dosing for children that will result in exposures similar to those found to be safe and effective in adults. Using doses selected based on the PK evaluation and agreed upon with the FDA, evaluate safety and treatment response of telaprevir in combination with pegylated interferon and ribavirin. Treatment response should be measured by sustained virologic response (SVR) in all pediatric subjects including previously untreated subjects and those who have failed a prior course of pegylated interferon and ribavirin therapy.

Final Protocol Submission:	September 2011 (completed)
Trial Completion:	September 2014
Final Report Submission:	February 2015

2052-2 Collect long-term safety data for subjects enrolled in the pediatric telaprevir safety and efficacy trial. Data collected should include at least 5 years of follow-up in order to characterize the long-term safety of telaprevir in pediatric patients, including growth assessment, sexual maturation and characterization of telaprevir resistance-associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission:	September 2011 (completed)
Trial Completion:	September 2018
Final Report Submission:	February 2019

Submit the protocols to your IND 71,832, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED**

PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Incivek® (telaprevir) was approved on May 23, 2011, we have become aware of a treatment emergent substitution at position 122 of the NS3/4A HCV protease that appeared to be associated with treatment failure in two subjects enrolled in Trial VX-950-C211, described in the submitted data. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risk of cross-resistance if HCV GT1a or GT1b with substitutions S122R, S122K, or S122T are less susceptible to Incivek® (telaprevir) or if these substitutions have an impact on Incivek® (telaprevir) susceptibility.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

Clinical Virology

2088-1 Conduct a study to assess the impact of NS3/4A substitutions S122T, S122R, and S122K on phenotypic susceptibility of telaprevir in the GT1a and GT1b HCV replicon systems.

The timetable you submitted on October 8, 2013, states that you will conduct this study according to the following schedule:

Study Completion:	05/2014
Final Report Submission:	06/2014

Submit the protocol to your IND 71,832, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Myung-Joo Patricia Hong, Regulatory Project Manager, 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

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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
10/28/2013