DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204671

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MSc, RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) dated and received April 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SOVALDI sofosbuvir tablets, 400 mg.

We acknowledge receipt of your amendments dated:

May 1, 2013
May 6, 2013
May 22, 2013
June 24, 2013
June 25, 2013
June 27, 2013
June 28, 2013
July 5, 2013
July 8, 2013
July 12, 2013
July 15, 2013
July 23, 2013
July 30, 2013 (2)
August 12, 2013
August 14, 2013
August 15, 2013
August 16, 2013
August 20, 2013
August 29, 2013
September 3, 2013 (2)
September 4, 2013 (2)
September 9, 2013 (2)
September 11, 2013
September 18, 2013
September 19, 2013
September 26, 2013
September 27, 2013
October 3, 2013 (3)
October 7, 2013
October 8, 2013
October 9, 2013
October 10, 2013
October 11, 2013 (2)
October 16, 2013
October 17, 2013 (2)
October 21, 2013 (2)
October 24, 2013
October 31, 2013
November 1, 2013 (2)
November 7, 2013
November 8, 2013
November 13, 2013 (2)
November 18, 2013
November 19, 2013
November 20, 2013 (2)
November 21, 2013 (2)
November 22, 2013
November 27, 2013
November 29, 2013
December 3, 2013
December 4, 2013
December 5, 2013
December 6, 2013

We also acknowledge receipt of your information related to sofosbuvir 400 mg tablets for your Gilead Access Program that was included in this application.

This new drug application provides for the use of SOVALDI (sofosbuvir) tablets as a component of a combination antiviral regimen for the treatment of chronic hepatitis C infection.

SOVALDI (sofosbuvir) 400 mg tablets have been granted a 24 month shelf life, when stored below 30ºC (86ºF) in the approved container closure system.

We have completed our review of this 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, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the : Immediate container labels submitted on December 05, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204671**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 birth to less than three years because necessary studies are impossible or highly impracticable. Moreover, spontaneous clearance is possible and very few patients in this age group require treatment.

We are deferring submission of your pediatric studies for ages 3 through 17 years for this application because this product is 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.

2110-1 Conduct a trial to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of SOVALDI (sofosbuvir) as a component of an antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

Final Protocol Submission:	10/2014
Trial Completion:	08/2018
Final Report Submission:	02/2019

2110-2 Collect and analyze long-term safety data for subjects enrolled in the pediatric SOVALDI (sofosbuvir) pharmacokinetic, safety and efficacy trial described in 2110-1. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of sofosbuvir in pediatric subjects, including growth assessment, sexual maturation and characterization of sofosbuvir resistance-associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission:	10/2014
Trial Completion:	02/2023
Final Report Submission:	08/2023

Submit the protocols to your IND 106,739, 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.

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 identify the unexpected serious risks of carcinogenicity, cardiac toxicity and treatment-emergent viral substitutions with SOVALDI (sofosbuvir) treatment durations greater than 12 weeks. Initially, the proposed duration of dosing for SOVALDI (sofosbuvir) for hepatitis C treatment was 12 weeks. During the review of the SOVALDI (sofosbuvir) application, FDA determined that longer durations of therapy resulted in higher efficacy. These durations dictate the need for carcinogenicity studies in accordance with regulations in 21 CFR 314.50 (d)(2) and the ICH M3(R2) and S1A guidances. In addition, we are aware of the finding of cardiac toxicity in one nonclinical study evaluating GS-9851 for seven days at a dose of 2000mg/kg. And finally, we are aware of viral variants with treatment-emergent substitutions isolated from patients who relapsed during SOVALDI (sofosbuvir) clinical trials. The impact of these substitutions on resistance to sofosbuvir is not completely understood.

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 these serious risks.

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

2110-3 Submit the final report for the 2-year mouse carcinogenicity study.

The timetable you submitted on December 05, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

2110-4 Submit the final report for the 2-year rat carcinogenicity study.

The timetable you submitted on December 05, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

2110-5 Conduct a short duration (7 to 14 days) rat toxicology study with sofosbuvir up to 2000 mg/kg/day to further evaluate the potential cardiac safety risk of sofosbuvir and its metabolites.

The timetable you submitted on December 05, 2013, states that you will conduct this study according to the following schedule:

Protocol Submission:	01/2014
Final Report Submission:	09/2014

2110-6 Determine the phenotypic susceptibility of sofosbuvir against:

HCV Genotype/Subtype	***NS5B Substitution***
Genotype 1a	*L159F* *L159F + L320F* *LI59F + C316N* *C316N, H, and F* *L320F, S282R, and L320F + S282R* *D61G* *D61G + N62H, D and N*
Genotype 1b	*L159F* *L159F+L320F* *L159F+C316N* *C316N, H, and F* *E440G*
Genotype 2b	*L159F* *L159F+L320F* *L159F+C316N*
Genotype 3a	*L159F* *L159F+L320F* *L159F+C316N* *K211R* *V321A* *P540L* *T542A*

The timetable you submitted on December 05, 2013, states that you will conduct this study according to the following schedule:

Study Completion:	05/2014
Final Report Submission:	08/2014

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of emergence of hepatitis C viral variants with resistance-associated substitutions to SOVALDI (sofosbuvir) and identify other unexpected serious risks due to prolonged treatment (greater than 24 weeks) with SOVALDI (sofosbuvir) in patients with hepatocellular carcinoma awaiting liver transplant. In addition, only a clinical trial will be sufficient to assess a known serious risk of elevated exposure to SOVALDI (sofosbuvir) levels in chronic hepatitis C patients with renal impairment in order to identify a safe and effective dose. Early data from a pharmacokinetic trial indicated that serum GS-331007 (sofosbuvir's metabolite) levels were markedly elevated in subjects with severe renal impairment or end-stage renal disease, resulting in exposures associated with serious and potentially life-threatening toxicities in nonclinical studies.

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

2110-7 Submit the final report and datasets including next generation sequencing for the ongoing trial P7977-2025 in order to identify treatment-emergent substitutions and to obtain additional safety and efficacy data in this population with hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation.

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/2013
Trial Completion:	06/2014
Final Report Submission:	12/2014

2110-8 Submit the final report and datasets for the ongoing trial GS-US-334-0154, entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir + RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for chronic hepatitis C patients with severely impaired renal function.

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	08/2016
Final Report Submission:	02/2017

2110-9 Submit the final report and datasets for the ongoing trial GS-US-334-0154, entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir + RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for chronic hepatitis C patients with ESRD.

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	02/2019
Final Report Submission:	08/2019

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of the following postmarketing commitments:

2110-10 Submit the final report and datasets for the ongoing trial GS-US-334-0133 (VALENCE), entitled, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Weeks in Treatment Naïve and Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection".

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	02/2013
Trial Completion:	01/2014
Final Report Submission:	07/2014

2110-11 Submit the final report and datasets for the ongoing trial GS-US-334-0123 (PHOTON-1), entitled, "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects".

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2012
Trial Completion:	02/2014
Final Report Submission:	08/2014

2110-12 Submit the final report and datasets for the ongoing trial GS-US-334-0109, entitled, "An Open-Label Study of GS-7977 + Ribavirin with or without Peginterferon Alfa-2a in Subjects with Chronic HCV Infection Who Participated in Prior Gilead HCV Studies".

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2013
Trial Completion:	12/2014
Final Report Submission:	06/2015

2110-13 Submit the final report and datasets for the ongoing trial GS-US-334-0153, entitled, "A Phase 3B Randomized, Open-Label, Multi-Center Trial Assessing Sofosbuvir + Ribavirin for 16 or 24 Weeks and Sofosbuvir + Pegylated Interferon + Ribavirin for 12 Weeks in Subjects with Genotype 2 or 3 Chronic HCV Infection".

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2013
Trial Completion:	03/2015
Final Report Submission:	09/2015

2110-14 Submit the final report and datasets for the ongoing trial GS-US-334-0126, entitled, "A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin for 24 Weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant".

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/2013
Trial Completion:	04/2014
Final Report Submission:	10/2014

2110-15 Submit the final report and datasets for the ongoing trial GS-US-334-0125, entitled, "A Phase 2, Multicenter, Open-Label, Randomized Study to Investigate the Safety and Efficacy of GS-7977 and Ribavirin Administered for 48 Weeks in Patients Infected with Chronic HCV with Cirrhosis and Portal Hypertension with or without Liver Decompensation".

The timetable you submitted on December 05, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2013
Trial Completion:	04/2015
Final Report Submission:	10/2015

2110-16 Submit an interim report from the ongoing study GS-US-248-0122, entitled, "A Long Term Follow-up Registry for Subjects Who Achieve a Sustained Virologic Response to Treatment in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection", with the three year follow-up data from: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), GS-US-334-0110 (NEUTRINO), GS-US-334-0133 (VALENCE), GS-US-334-0123 (PHOTON-1).

The timetable you submitted on December 05, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Trial Completion:	05/2017
Final Report Submission:	11/2017

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will

be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Edward M Cox, MD, MPH
Director
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/

EDWARD M COX
12/06/2013