

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204671Orig1s000

OTHER REVIEW(S)

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

PMR/PMC Development Template

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

NDA/BLA # NDA 204671
Product Name: Sofosbuvir

PMR/PMC Description: PREA PMR for pediatric population ages 3 to less than 18 years of age.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/2014</u>
	Study/Trial Completion:	<u>02/2023</u>
	Final Report Submission:	<u>08/2023</u>
	Other:	_____

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

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

Adult studies are ready for approval.

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

The study is a deferred pediatric study under PREA for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 through 17 years of age. The trial will collect long-term safety data for subjects enrolled in the pediatric SOVALDI (sofosbuvir) pharmacokinetic, safety and efficacy trial(s). 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.

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

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- Animal Efficacy Rule
- Pediatric Research Equity Act
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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
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Collect and analyze long-term safety data for subjects enrolled in the pediatric SOVALDI (sofosbuvir) pharmacokinetic, safety and efficacy trial(s). 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.

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Dosing trials
Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

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Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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 There is not enough existing information to assess these risks
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 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

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SOHAIL MOSADDEGH
12/06/2013

The final study report and datasets including next generation sequencing for the ongoing trial P7977-2025 are requested 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. This population is receiving sofosbuvir plus ribavirin (SOF+RBV) treatment up to 48 weeks or until transplantation, a longer duration than evaluated in the SOVALDI Phase 3 registrational trials. Initially, treatment was up to 24 weeks or until transplant; however, a total of 11 of 15 subjects (73%) who completed 24 weeks of SOF+RBV treatment relapsed in the pre-transplant phase. The virologic relapse rate after 24 weeks of treatment in this patient population suggested a longer treatment duration may be indicated to achieve HCV RNA < LLOQ at the time of transplant. This finding led to a protocol amendment to extend the treatment duration from 24 weeks to 48 weeks or to the time of transplant. A limited number of subjects have received SOF+RBV treatment for 48 weeks; therefore, results from this trial will assess other unexpected serious events due to an extended treatment duration (greater than 24 weeks).

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Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Submit the final study 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
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Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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2 year carcinogenicity studies in rats and mice

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Determine the phenotypic susceptibility of sofosbuvir against the following HCV replicons:

HCV replicons	Substitution
Genotype 1a	L159F L159F + L320F L159F + 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

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Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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Obtain dosing recommendations for chronic HCV patients with severely impaired renal function.

The Phase 1 trial, P7977-0915 entitled, “An Open-Label Study of Pharmacokinetics of Single Oral Doses of PSI-7977 (sofosbuvir) in Subjects with Varying Degrees of Renal Function” , was a single dose sofosbuvir 400 mg pharmacokinetic (PK) renal impairment trial. Results from this trial demonstrated that in subjects with severe renal insufficiency, defined as eGRF <30 mL/min/1.73m², the sofosbuvir AUC was increased 171%, and the GS-331007 AUC was increased 451%. These exposures exceed safety margins observed in nonclinical studies.

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”, is designed to be conducted in 2 parts. Part 1 will enroll approximately 20 subjects with severe renal insufficiency.

- 10 subjects will receive sofosbuvir (SOF) 200 mg QD + RBV 200 mg QD for 24 weeks.
- Following review of safety, efficacy and PK data through post-treatment Week 4 of the Part 1 SOF 200 mg group, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.

Part 2 will enroll approximately 20 subjects on dialysis following review of safety, efficacy and PK data through post-treatment Week 4 of Part 1 SOF 400 mg group.

- 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Following review of safety, efficacy and PK data through post-treatment Week 4 of the Part 2 SOF 200 mg group, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.

The GS-US_334-0154 final study report and datasets are identified as a PMR in order to provide dosing recommendations for chronic hepatitis C patients with severely impaired renal function. Because P7977-0915 data indicated that serum sofosbuvir metabolite levels were markedly elevated in renally impaired subjects, resulting in exposures for which serious and potentially life-threatening toxicities were observed in nonclinical studies, we have determined it is necessary to identify a safe and effective dose of SOVALDI (sofosbuvir) in chronic hepatitis C patients with renal impairment.

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Genotype 1 or 3 HCV-infected subjects with renal insufficiency
--

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

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

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

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

Obtain dosing recommendations for chronic HCV patients with ESRD.

The Phase 1 trial, P7977-0915 entitled, “An Open-Label Study of Pharmacokinetics of Single Oral Doses of PSI-7977 (sofosbuvir) in Subjects with Varying Degrees of Renal Function”, was a single dose sofosbuvir 400 mg pharmacokinetic (PK) renal impairment trial. Results from this trial demonstrated that in subjects with ESRD when sofosbuvir was dosed 1 hour before dialysis, the sofosbuvir AUC was increased 28%, and the GS-331007 AUC was increased 1280%. In subjects with ESRD when sofosbuvir was dosed 1 hour after dialysis, the sofosbuvir AUC was increased 60%, and the GS-331007 AUC was increased 2070%. These exposures exceed safety margins observed in nonclinical studies.

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”, is designed to be conducted in 2 parts. Part 1 will enroll approximately 20 subjects with severe renal insufficiency.

- 10 subjects will receive sofosbuvir (SOF) 200 mg QD + RBV 200 mg QD for 24 weeks.
- Following review of safety, efficacy and PK data through post-treatment Week 4 of the Part 1 SOF 200 mg group, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.

Part 2 will enroll approximately 20 subjects on dialysis following review of safety, efficacy and PK data through post-treatment Week 4 of Part 1 SOF 400 mg group.

- 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Following review of safety, efficacy and PK data through post-treatment Week 4 of the Part 2 SOF 200 mg group, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.

The GS-US_334-0154 final study report and datasets are identified as a PMR in order to provide dosing recommendations for chronic hepatitis C patients with ESRD. Because P7977-0915 data indicated that serum sofosbuvir metabolite levels were markedly elevated in renally impaired subjects, resulting in exposures for which serious and potentially life-threatening toxicities were observed in nonclinical studies, we have determined it is necessary to identify a safe and effective dose of SOVALDI (sofosbuvir) in chronic hepatitis C patients with ESRD.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Genotype 1 or 3 HCV-infected subjects with renal insufficiency

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

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

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

PMR/PMC Development Template

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

NDA/BLA # NDA 204671
Product Name: Sofosbuvir

PMR/PMC Description: Final Study report for GS-US-334-0133 (VALENCE)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Completed
	Study/Trial Completion:	01/2014
	Final Report Submission:	07/2014
	Other:	_____

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

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

Subsequent to the Primary Clinical Review, the Applicant made us aware of the emerging data from 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". This trial is a non-IND trial being conducted in Europe.

The observed sustained virologic response rates measured at 12 weeks after treatment completion (SVR12) for HCV genotype 3 subjects were consistently lower than HCV genotype 2 subjects across all three trials (FISSION, POSITRON, FUSION) submitted for original NDA review. Reduced response rates in genotype 3 subjects were driven by high relapse rates, indicating that extending the duration of therapy may improve SVR. The collective evidence from the available Phase 3 trials indicated that 12 or 16 weeks of SOF+RBV is not the optimal regimen for HCV genotype 3 patients and the SVR12 rates can be further optimized by longer treatment duration in genotype 3 patient population.

The highlights of the GS-US-334-0133 (VALENCE) data shared by the Applicant appeared promising and supported longer treatment duration (24 weeks of sofosbuvir and ribavirin) for genotype 3 subjects. From a public health perspective, approving a suboptimal regimen when the emerging data is already available for 24 week treatment duration would not be beneficial for patients and would unduly expose patients to a suboptimal therapy. Taking these factors into consideration, a decision was made to review the currently available interim data from VALENCE trial during current review cycle rather than waiting for the trial completion.

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

Interim data from this trial supported dosing recommendations in one subpopulation; therefore, submission of the final study report and datasets for GS-US-334-0133 (VALENCE) is designated as a PMC by the review team to further ensure consistency of the trial results.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Submit the final study 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".

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

-
- Other
-

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

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

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 - There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

Determine the phenotypic susceptibility of sofosbuvir against the following HCV replicons:

HCV replicons	Substitution
Genotype 1a	L159F L159F + L320F L159F + 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

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

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

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

PMR/PMC Development Template

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

NDA/BLA # NDA 204671
Product Name: Sofosbuvir

PMR/PMC Description: Final Study report for GS-US-334-0109

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Completed
	Study/Trial Completion:	<u>12/2014</u>
	Final Report Submission:	<u>06/2015</u>
	Other: _____	_____

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

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

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”, is an ongoing open-label trial evaluating sofosbuvir in combination with ribavirin with or without peginterferon alfa-2a in subjects with chronic HCV infection who participated in prior HCV trials conducted by Gilead. Hence, this trial could not be completed pre-approval.

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

Clinical HCV trials have generally categorized patients as treatment-naïve or treatment-experienced based upon their prior virologic response to a pegylated interferon and ribavirin (PEG/RBV) regimen. During an End-of-Phase 2 meeting (June 5, 2012), when asked about sofosbuvir development plans in prior PEG/RBV treatment-experienced patients, the Applicant stated they intended to identify the best regimen in HCV genotype 1 treatment-naïve patients, then would proceed in trials in the more difficult to treat patients including those who failed prior PEG/RBV treatment. Therefore, HCV genotype 1 patients who failed prior treatment with PEG/RBV were not specifically studied in the sofosbuvir development program supporting this NDA.

During the review we recognized this population was in need of new therapies and, particularly due to the high overall SVR12 rate observed in NEUTRINO (sofosbuvir plus PEG/RBV for 12 weeks), attempted to estimate response rates in prior PEG/RBV nonresponders using existing data. Modeling and simulation analyses were conducted by the sofosbuvir review team to address this issue. Two of the exploratory analyses were presented at the Antiviral Drugs Advisory Committee Meeting on October 25, 2013, including one selecting HCV genotype 1 treatment-naïve subjects from NEUTRINO with the following three baseline factors which are representative of lower SVR response to PEG/RBV treatment: IL28B non-CC genotype, baseline HCV RNA viral load >800,000 IU/mL and METAVIR score of F3-F4. These analyses provided supportive evidence that sofosbuvir plus PEG/RBV for 12 weeks may be an effective treatment option in HCV genotype 1 prior PEG/RBV treatment failures.

As described in more detail below, GS-US-334-0109 is an ongoing, open-label trial offering sofosbuvir-based treatment to prior Gilead trial participants, including HCV genotype 1 subjects who did not achieve an SVR following treatment with PEG/RBV +/- combination with other direct acting antiviral agents. These subjects have received retreatment with sofosbuvir plus PEG/RBV for 12 weeks (Arm 3). Therefore, data from trial GS-US-334-0109 would provide information in HCV genotype 1 prior PEG/RBV nonresponders treated with sofosbuvir plus PEG/RBV for 12 weeks to support the prior modeling and simulation analyses performed during this NDA review cycle.

More generally, potentially eligible subjects for this open-label trial include, but are not limited to those in the following categories:

- received placebo or PEG+RBV in a control arm
- previously participated in a Gilead-sponsored HCV study and did not attain SVR24 on a regimen containing:
 - o GS-7977+RBV
 - o PEG and/or RBV in combination with one or more Gilead investigational DAAs (e.g., GS-5885, GS-9451, GS-9256, GS-9190)

Treatment arms include:

- Arm 1 (genotype 2 HCV-infected subjects): sofosbuvir + RBV for 12 weeks
- Arm 2 (genotype 2 and 3 HCV-infected subjects): sofosbuvir + RBV for 24 weeks
- Arm 3 (all genotypes of HCV-infected subjects): sofosbuvir + RBV + PEG for 12 weeks

Therefore, in addition to the data in HCV genotype 1 prior PEG/RBV nonresponders, GS-US-334-0109 data may provide information about use of sofosbuvir in subjects who previously failed sofosbuvir-based regimens.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Submit the final study 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".

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

The emerging data from Phase 3 trials in HCV genotype 3 subjects indicated that sofosbuvir in combination with ribavirin (SOF+RBV) for 12-16 weeks duration was not optimal due to observed lower sustained virologic response rates (SVR12) and high relapse rates. 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” was designed and initiated by the Applicant to evaluate longer duration (24 weeks) of sofosbuvir and ribavirin (SOF+RBV) therapy and the addition of pegylated interferon to the SOF+RBV regimen (12 weeks) to optimize the response rates. Data became available from a subsequent non-IND European trial, VALENCE, which supported a SOF+RBV 24 week duration in the genotype 3 population. The overall SVR12 rate for all genotype 3 subjects treated with SOF+RBV for 24 weeks was higher (84%) than observed in prior trials with SOF+RBV 12-16 week durations. Within particular subgroups (e.g., genotype 3 treatment-experienced subjects with cirrhosis), however, similar SVR12 rates were observed across trials with differing SOF+RBV treatment durations. Possible explanations for this observation include differences in baseline factors between the trials in this cirrhotic subgroup, a lack of benefit from further extending SOF+RBV duration, or a need for another antiviral agent in the regimen to further improve treatment response.

This ongoing multicenter, international (including U.S. sites), randomized trial will provide a direct comparison of 16 and 24 weeks of SOF+RBV, and provide a comparison with 12 weeks of SOF+RBV with pegylated interferon in the genotype 3 population and also in the genotype 2 treatment-experienced cirrhotic population. This trial will allow data comparison between different geographic regions as well.

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

As noted above, the final study 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” may further optimize the treatment recommendations for these patient populations. In addition, this ongoing multicenter, international (including U.S. sites), randomized trial will provide a direct comparison of 16 and 24 weeks of SOF+RBV, and provide a comparison with 12 weeks of SOF+RBV with pegylated interferon in the genotype 3 population and also in the genotype 2 treatment-experienced cirrhotic population. This trial will allow data comparison between different geographic regions as well.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Submit the final study 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.

Required

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

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
12/06/2013

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If not a PMR, skip to 4.

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

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

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

Submit the final study 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".

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

Submit the final study 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”.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials
Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

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

Other

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

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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12/06/2013

An interim study report from the ongoing trial 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) will provide long-term data on the durability of treatment response, including data from non-interferon-containing regimens.

The primary objective of this registry is to assess the durability of sustained virologic response (SVR) following treatment in a Gilead-sponsored trial. The secondary objectives of this registry are to determine whether subsequent detection of HCV RNA in subjects who relapse following SVR, represents the re-emergence of pre-existing virus, the development of resistance mutations, or whether it is due to re-infection; to assess clinical progression of liver disease; and to screen for the development of hepatocellular carcinoma (HCC). Once enrolled, subjects will be followed for up to 3 years. Visits will occur at Baseline and then at Weeks 24, 48, 72, 96, 120 and 144. At each visit, subjects will have blood drawn for plasma HCV RNA quantification, liver function tests, platelets, coagulation test, α -fetoprotein, and a quality of life survey will be completed. If HCV RNA is detected, the subject will have a repeat blood sample drawn for confirmation. If HCV RNA is confirmed the subject will be withdrawn from the Registry. If the confirmed HCV RNA is > 1000 IU/ml, viral sequence analysis will be performed.

The listed six trials are the Phase 3 registrational trials supporting dosing and administration recommendations.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Submit an interim study report from the ongoing trial 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)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

- Other

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

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

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

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SOHAIL MOSADDEGH
12/06/2013

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Conduct a short duration (7 to 14 days) rat study with sofosbuvir up to 2000 mg/kg/day.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2014</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>09/2014</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Cardiac toxicity was observed in a single rat study when a mixture of two isomers (one isomer being sofosbuvir) was administered at a dose of 2000 mg/kg/day for seven days. Cardiac toxicity was not observed in any other species or in any other nonclinical study in which sofosbuvir and not the mixture of two isomers was administered. In addition, FDA just received a second case report of cardiomyopathy in a post-liver transplant patient receiving sofosbuvir. The cardiomyopathy is a well described complication of post-transplant liver cirrhosis, however, there is a temporal relationship to sofosbuvir administration in both cases.

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

To better characterize the potential of sofosbuvir and/or it's major metabolite to cause cardiac toxicity in a rat model.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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SOHAIL MOSADDEGH
12/06/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	SOVALDI (sofosbuvir) tablets, for oral use
Applicant	Gilead Sciences, Inc.
Application/Supplement Number	NDA 204671
Type of Application	Original Submission (NME)
Indication(s)	For the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen
Office/Division	OAP/DAVP
Division Project Manager	Poonam Mishra
Date FDA Received Application	April 8, 2013
Goal Date	December 8, 2013
Date PI Received by SEALD	November 27, 2013
SEALD Review Date	November 29, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *HL is greater than 1/2 page. DAVP will grant waiver for 1/2 page HL requirement.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Dosage and Administration heading in HL is not bolded.*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space is missing before each major heading in HL. Insert. In addition, there is white space between HL Heading and HL Limitation Statement; there is also white space between the product title and initial U.S. approval. There should be no white space for these two HL areas. See Appendix A.*

Selected Requirements of Prescribing Information

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S.**

Selected Requirements of Prescribing Information

Approval:” followed by the **4-digit year**.

Comment: 4-digit year is missing. Must read "2013" and not "YYYY."

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

Selected Requirements of Prescribing Information

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Revision date is missing. Must read "12/2013," not "MM/YYYY."*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: TOC subsection headings (Warnings and Precautions 5.1 and Use in Specific Populations 8.11) do not match the FPI subsection headings for 5.1 and 8.11. Please correct.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: For subsection 5.2, the cross reference should read "[see Drug Interactions (7.2)]," not "[See Drug Interactions (7), Table 5]."

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION**". This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JEANNE M DELASKO
11/29/2013

DEBRA C BEITZELL
11/29/2013
Debra Beitzell signing for Sandra Kweder.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 26, 2013

To: Linda Onaga, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: L. Sheneé Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 204671
OPDP labeling comments for Sofosbuvir tablets, for oral use
Labeling Review

OPDP has reviewed the proposed package insert (PI), patient package insert (PPI) and carton/container labeling for Sofosbuvir tablets, for oral use (Sofosbuvir) that was submitted for consult on April 24, 2013. Comments on the proposed PI are based on the version sent via email from Linda Onaga (RPM) on November 19, 2013 entitled "SOF LABEL DAVP Edits 11-19-13 sub complete.doc".

Comments regarding the PI are provided on the marked version below.

Please note that comments on the PPI will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP). We have no comments on the draft carton/container labeling accessed from the following EDR location, \\CDSESUB1\EVSPROD\NDA204671\204671.enx

Thank you for the opportunity to comment.

If you have any questions, please contact Sheneé' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
11/26/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 26, 2013

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN,BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
L. Shenee' Toombs, Pharm. D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (sofosbuvir)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 204671

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On April 6, 2013, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 204671 for TRADENAME (sofosbuvir) tablets, with the proposed indication for the treatment of chronic hepatitis C (CHC) infection.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Antiviral Products (DAVP) on April 18, 2013 and April 24, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (sofosbuvir) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (sofosbuvir) PPI received on April 8, 2013 and received by DMPP and OPDP on November 19, 2013.
- Draft TRADENAME (sofosbuvir) Prescribing Information (PI) received on April 8, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 19, 2013.
- Approved OLYSIO (simeprevir) comparator labeling dated November 22, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

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

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
11/26/2013

LATOYA S TOOMBS
11/26/2013

BARBARA A FULLER
11/26/2013

LASHAWN M GRIFFITHS
11/26/2013

DAVP 11/25/13 edits



Sofosbuvir (SOF; GS-7977)

NDA 204671

Module 1.11.3

**Response to Proposed Postmarketing Requirements and Postmarketing
Commitments Dated 21 November 2013**

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

22 November 2013

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3. APPENDICES 11

 Appendix 1. FDA Correspondence dated 21 November 2013 (Reference ID
3410966) 11

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/s/

SOHAIL MOSADDEGH
11/25/2013



Memorandum

Date: Nov 20, 2013

From: Krishna Ghosh, Compliance Officer
Generic Drug Manufacturing Assessment Branch (GDMAB)

Compliance recommendation for NDA 204671 (Sofosbuvir)

Through: Tara Goen, Acting Branch Chief
New Drug Assessment Branch (NDMAB)
Division of Good Manufacturing Practice Assessment (DGMPA)

To: NDA 204671 file

Applicant: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Control Testing Lab: Gilead Sciences Inc.
333 Lakeside Drive
Foster City, CA 94404
FEI 1000523075

The Office of Manufacturing and Product Quality (OMPQ) has conducted a review of the 483 observations for Gilead Sciences Inc., Foster City, CA. This site is named as the testing lab for the API and finished dosage for Sofosbuvir NDA 204671. An inspection in support of listed operations per CPGM 7346.842 and KTM was initiated by SAN-DO on September 23, 2013. The profile class covered was CTL (contract testing laboratory).

Background: Gilead Foster City had an inspection from (b) (4) and provided PAI inspectional coverage for (b) (4) at the Gilead contract testing lab(FEI:1000523075) located in Foster City, CA. Areas covered during the inspection included, but were not limited to the following: Suitability and validation of analytical test methods for (b) (4) stability program, analytical equipment calibration, cleaning procedures, process validation studies, quality assurance and documentation control.

Several deficiencies were observed during the (b) (4) inspection and a FDA-483 was issued at the close of the inspection. The firm failed to report the various changes to

analytical test methods for the API and final drug products for (b) (4) during the course of the stability studies conducted by the firm. The firm also failed to conduct adequate bridging studies (analytical assay comparability/equivalency studies) for the various changes made to the assays. Additional deficiencies were noted for the following- stability program, process validation studies, calibration of analytical instruments, verification of USP analytical tests for intended use, records controls, analytical equipment usage and controls. (b) (4)

(b) (4)
(b) (4)
the FDA 483 issued on October 9, 2013 for PAI inspection of NDA 204671 (Sofosbuvir) and post market (NDA 203000 Stribild) inspection.

NDA 204671 (Sofosbuvir)

There are eleven (11) globally located manufacturing, testing and packaging sites associated with the current application for the API and the finished drug product Sofosbuvir. CDER OC had some serious concerns with two of the sites (b) (4) and the Gilead testing site (FEI 1000523075, Foster City, CA). At (b) (4) EDQM inspectional findings (b) (4) uncovered serious data reliability and integrity issues along with GMP violations which were shared with FDA. The concerns with Gilead testing site (Foster City, CA) were due to the pending OAI status from the (b) (4)

During the late cycle meeting with Gilead, Gilead agreed to amend the application and remove (b) (4) as an API manufacturing site.

Gilead PAI Inspection (9/23- 10/9/2013)

The most recent inspection included a PAI for Sofosbuvir and post approval inspection for Stribild and was conducted from 9/23- 10/09/2013. Major deficiencies were observed in the stability study program due to lack of GMP process controls along with additional repeat GMP violations from the previous inspections at this site. Furthermore, the firm has failed to implement systemic corrective actions for several of the FDA 483 observations identified during the April 2013 inspection. FDA 483 was issued to the firm at the close of the inspection on 10/09/2013.

The following are some of the major deficiencies that were identified during the current inspection:

1. The firm has failed to demonstrate that the stability studies for Sofosbuvir (NDA 204671-12SB001R, 12SB002R and 12SB003R) were conducted under GMP regulations with adequate process controls.

- Stability lots 12SB002R and 12SB003R could not be reconciled. Two samples from each lot were discarded without any rationale or adequate justification.
- Discrepancy was noted with regards to the exact transfer dates of stability samples (lots# 12SB001R, 12SB002R and 12SB003R) within the analytical testing group, GMP warehouse and the LIMS (Laboratory Instrumentation and Integration system) which is used by the analysts for test data recording. This issue raises significant concerns with regards to data reliability and reporting.

2. The firm has failed to initiate stability studies within an acceptable time frame after receipt at the Gilead Foster City from various manufacturing sites. A standard operating procedure has not been implemented to define and control the process and initiate the stability studies in a timely manner. Due to inconsistency with time zero testing for the different lots, any failures during stability studies may pose some challenges and the root cause may not be correctly identified. This is a repeat violation that was identified during the April 2013 inspection (**Observation #7 April 2013 and July 2011 inspection**)

Table 1.

Product	Lot Number	Manuf. Date	Pkg. Date	Placed on stability
Sofosbuvir API	GS-7977(6)-6-12001/2 GS-7977(6)-6-12002/1	(b) (4)		
Sofosbuvir (Tablets)	MXHS, MXHT, MXHV			

3. The firm failed to reconcile the stability samples in eight (8) out of eleven (11) of their stability chambers under their current stability program for all their products. The firm identified 143 individual discrepancies during the reconciliation process conducted by the firm as a part of investigation by the FDA investigators. These findings were recorded in a deviation report DV13-214 by the firm during the inspection which clearly demonstrates that the firm has failed to implement adequate process controls and internal QA audits for their stability program. The following general comments for observation #1 in the FDA 483 were described by the investigators during the conference call with CDER/OC on October 18, 2013:

- The number of stability samples received by Gilead Foster City from the various API and final drug product manufacturing sites and placed on the stability program at the initiation of a particular stability study could not be accounted for due to missing documentation (**Missing documentation of stability samples is a repeat observation #4, April 2013**)
- No sample logs were implemented to account for the test samples taken out of the chambers during each test intervals.

- Number of stability samples for a particular study could not be determined at any given time through a controlled inventory management system without physically counting the samples in the stability chambers
 - No deviation reports were generated due to changes to stability protocol. Analysts added new samples to inventory and changed testing locations by shipping samples to contract testing sites without any oversight or approvals for the deviations to the stability protocols. **(Repeat Observation #7, April 2013)**
4. The firm performed inadequate “Out of Specification investigations” for Sofosbuvir API and finished product tablets
- Lots GS-7977(6)-12002/1, 7977-CC-2P and GS-7977(6)-12001/2 were tested on 1/15/2013. The laboratory investigation report LI13-003 recorded that the tests were performed according to procedure F13-0123 and the results were invalidated due to instrument failure of the (b) (4) (b) (4). No instrument failure reports were found or recorded. The sample was not retested until after one month Feb 6, 2013 by another procedure F13-0397 and found to pass the test. No explanation for the lag time in testing was obtained from the analyst.
 - Finished product stability lots DC1208B, DC1214B and DC1209B was tested and a failure investigation report was generated in Jan 2013 (13-007) and the test results failed due to “ low strength results/low suspect results” due to sample extraction technique applied by the analyst. The analyst was trained as part of corrective action and the investigation closed out. The same failure occurred again in March 2013 (13-021) which demonstrated that the root cause and the corrective action was inadequate to prevent the failure of the test.
5. The firm lacks adequate laboratory process controls and procedures with regards to the following:
- The logbooks and instrument usage logs are not issued, controlled or audited by the QA/QC department. Data audit logs are not reviewed or saved as controlled records inadequate corrective actions have been implemented by the firm. **(This is repeat FDA 483 observation #9).**
 - The firm has failed to implement a standard operating procedure for shipment of QC test samples to the contract manufacturing testing site with TempTales. The procedure was submitted to the investigators on 10/01/13 after the deficiency was observed. The submitted procedure did not clearly identify the placement of the TempTales on the box.
 - The firm does not have a defined naming convention procedure for the QC test samples. The random naming process does not provide a clear traceability of a particular sample being tested multiple times. Re-injection or re-analysis cannot be evaluated without reviewing each sample set individually.

CDER/OC/OMPQ/NDMAB Analysis:

Following are some of the concerns with the testing capability and readiness of the firm to continue the following activities- stability testing program and QC testing for the drug substance and the final product for NDA 204671:

- The firm continues to operate as in product development. It lacks GMP laboratory process controls for the stability study program to ensure reliable and accurate data and records are generated to support the drug applications submitted to the agency. **This is repeat observation.**
- The firm lacks adequate computer and electronic data acquisition controls to meet the 21 CFR Part 11 compliance for the following analytical equipment: Karl Fischer moisture analyzer, UV spectrophotometer, FTIR and DSC. They lack GMP controls related to audit trails, raw data records and record retention. Lack of such controls prevents the agency to effectively determine the data reliability/integrity of the data submitted to support the drug application. **Inadequate corrective action for Karl Fischer equipment was observed (Observation 3, April 2013)**
- The firm demonstrated poor record controls, such as the lack of QA oversight and control of log books and instrument use logs to initiate failure investigations and document calibrations, maintenance and usages. **This is a repeat observation.**
- The firm has repeatedly failed to conduct equipment qualifications and assay verifications for intended use for the USP assays. **This is a repeat observation (Observation 2).**
- The current “Out of Specification” investigations are inadequate and incomplete. The root cause identification process does not identify accurate root causes to ensure that equipment and sample test failures can be adequately identified and repeat failures can be prevented.
- Some of the corrective action plans implemented by the firm are not adequate in that they lack a systemic approach. The firm needs to evaluate the various GMP and product related observations from the previous and current inspection and implement systemic corrective actions for all the FDA regulated products .

FDA Regulatory Strategy for approval of NDA 204671

A. Removal of ST Pharm from Application

FDA requested Gilead Sciences to remove (b) (4) from the application due to serious data integrity violations reported by EDQM inspectional report and inadequate corrective action response received by FDA from (b) (4). Gilead removed (b) (4) from the application before the import alert was issued by FDA on (b) (4) for all the products manufactured by the firm.

B. Removal of Gilead Foster City from Application

Due to serious concerns regarding lack of GMP process controls, inadequate corrective actions and continued issues with the Stability program at Gilead Foster City site, CDER/OC/DGMPA developed a regulatory strategy with the two options listed below as a path forward to approve the application. These options were provided to Gilead via email on October 28, 2013. A conference call was held on October 29, 2013 with the Gilead management team to discuss the two options listed below:

Option 1 (Gilead Foster City - Facility Withdrawal)

Remove Gilead Foster City as a testing site for Drug Substance and Drug Product release and stability testing operations from the application. Transfer stability studies along with API and final product testing responsibilities to a CGMP compliant testing lab already listed in the application [REDACTED] (b) (4)

Option 2 (Post-Marketing Commitment)

1. Gilead will retain an expert party that will, prior to the distribution of each batch, review all records for all listed testing operations. For Gilead Foster City the expert will review all raw data and equipment audit trails, logbooks and usage logs, out of specification investigations, invalidated test results and retest plans, equipment failures, maintenance and calibrations records, QC testing data (raw data, chromatograms, print outs and calculations) and either:
 - A. Certify that, based upon the expert's review of all data derived from all manufacturing and testing sites, no deviations occurred during the testing of the batch that, in the expert's professional opinion, would, during its labeled expiration period, adversely affect the safety, identity, strength, quality, or purity of the batch or cause the batch to fail to meet any and all applicable approved specifications established in its application; **or**
 - B. If the expert is unable to make the certification described in subparagraph A above, deliver a written report to Gilead, explaining the expert's reasons for not so certifying the batch, which report shall include:
 - List of deviations, adequacy of investigations and a scientific analyses of laboratory tests failures with appropriate root cause determinations and timely corrective actions
 - Justification for the specific basis for invalidating test results, retesting products or testing of new samples when indicated

- Assessment on the effect of deviations on the safety, identity, strength, quality, or purity of the batch the QA/QC has failed to address during review of batch records/test results
- Determination on batch disposition

Additionally, review and certify all testing data associated with the ongoing stability studies for Sofosbuvir and ensure that the stability studies are conducted in a timely manner under GMP requirements. Review the adequacy of the corrective actions associated with the stability program.

Gilead shall not release batches for distribution until third party certification is received, however may ship product for further processing or holding under quarantine. Gilead shall provide summary results of the expert's reports on a quarterly basis to FDA/CDER/OC/OMPQ following approval. Copies of reports should be maintained at the Foster City facility and be made immediately available upon request.

At the October 29, 2013 teleconference, Gilead agreed to Option #1 and submitted an amendment to remove Gilead Foster City as a testing site for NDA 204671.

Current Gilead Foster City Status

Gilead Foster City will still perform the final QA release function for the final product Sofosbuvir. All API and final product testing will be performed by the API and final product manufacturing sites which were inspected and found acceptable. The stability testing program for the API and final product will be performed by a GMP compliant contract testing lab which was submitted in the application.

CDER/OC/OMPQ/DGMPA recommendation:

Gilead has removed (b) (4) and Gilead Foster City testing sites from the application so CDER/OC/OMPQ is recommending to approve the NDA.

If you have any questions, please contact me at 301-796-2644, or by email at Krishnakali.Ghosh@fda.hhs.gov.

Krishna Ghosh, Ph.D.
Compliance Officer
CDER/OC/OMPQ/DGMPA/GDMAB
Cc:

CMS# 71546

HFD-320 Tara Goen, Acting BC, NDMAB

To: San Francisco District (SAN-DO) Pre-Approval Manager, William (Bill) Millard

George Lunn ,CDER/ONDQA

Fuqiang Liu, CDER/ONDQA

Rapti Madurawe, CDER/ONDQA

Stephen Miller, CDER/ONDQA

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

/s/

KRISHNA GHOSH
11/21/2013

TARA R GOOEN
11/22/2013

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 204671/000
Code: 530
Priority: 1
Stamp Date: 08-APR-2013
PDUFA Date: 08-DEC-2013
Action Goal:
District Goal: 08-AUG-2013

Sponsor: GILEAD SCIENCES INC
 333 LAKESIDE DR
 FOSTER CITY, CA 94404
Brand Name: PSI-7977
Estab. Name:
Generic Name: SOFOSBUVIR
Product Number; Dosage Form; Ingredient; Strengths
 001; TABLET; SOFOSBUVIR; 400MG

FDA Contacts:	G. LUNN	Prod Qual Reviewer		3017961701
	S. DONALD	Micro Reviewer	(HFD-805)	3017960586
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	L. ONAGA	Regulatory Project Mgr	(HFD-530)	3017960759
	R. MADURAWA	Team Leader		3017961408

Overall Recommendation:	ACCEPTABLE	on 12-NOV-2013	by M. HEAYN	(HFD-320)	3017964753
	PENDING	on 21-AUG-2013	by EES_PROD		
	PENDING	on 13-JUN-2013	by EES_PROD		
	PENDING	on 09-MAY-2013	by EES_PROD		
	PENDING	on 26-APR-2013	by EES_PROD		
	PENDING	on 22-APR-2013	by EES_PROD		
	PENDING	on 22-APR-2013	by EES_PROD		
	PENDING	on 22-APR-2013	by EES_PROD		
	PENDING	on 22-APR-2013	by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-AUG-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-APR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-AUG-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-MAY-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: **CFN:** 3006709727 **FEI:** 3006709727
GILEAD SCIENCES LIMITED
IDA BUSINESS & TECHNOLOGY PARK
CARRIGTOHILL, IRELAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 2082946 **FEI:** 2082946
GILEAD SCIENCES, INC.
SAN DIMAS, UNITED STATES 917732957

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-MAY-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-APR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-AUG-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 23, 2013

Reviewer: Morgan Walker, PharmD, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Deputy Director: Carol Holquist, RPh.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Tradename (Sofosbuvir) Tablets, 400 mg

Application Type/Number: NDA 204671

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2013-874

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Sofosbuvir Tablets, 400 mg (NDA 204671) for areas of vulnerability that could lead to medication errors. Of note, the Applicant submitted carton labeling and container labels for the Gilead Access Program. These products will not be marketed in the United States; therefore DMEPA will not review them at this time.

1.1 PRODUCT INFORMATION

The following product information is provided in the April 8, 2013 submission:

- Active ingredient: Sofosbuvir
- Indication: For use in combination with either ribavirin alone, or ribavirin and peginterferon alfa, for the treatment of chronic hepatitis C.
- Route: Oral
- Dosage Form: Tablet
- Strengths: 400 mg
- Dose and Frequency: The recommended dose is one 400 mg tablet, taken orally, once daily with or without food.
- How Supplied: 28-count bottles
- Storage: Store below 30°C (86°F)
- Applicant: Gilead Sciences

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Sofosbuvir labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted April 8, 2013 (Appendix B)
- Insert Labeling submitted April 8, 2013

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the insert labeling is acceptable from a medication error perspective. However, we request the label be revised as described below prior to approval of this NDA:

- A. Comments to the Applicant
 - a. Relocate the dosage form “Tablets” to appear on the same line next to the active ingredient “sofosbuvir” as follows:

(sofosbuvir) Tablets

400 mg

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

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

/s/

JAMIE C WILKINS PARKER on behalf of MORGAN A WALKER
09/23/2013

JAMIE C WILKINS PARKER
09/23/2013

CAROL A HOLQUIST
09/24/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 21, 2013

TO: Linda Onaga, MPH, Regulatory Health Project Manager
Poonam Mishra M.D., Medical Officer
Division of Antiviral Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Janice Pohlman, M.D., M.P.H. covering for Kassa Ayalew, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204-671

APPLICANT: Gilead Sciences, Inc.

DRUG: Sofosbuvir (GS-7977)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review
INDICATION: Treatment of chronic HCV- infected adults
CONSULTATION REQUEST DATE: May 7, 2013
DIVISION ACTION GOAL DATE: December 6, 2013
PDUFA DATE: December 6, 2013
INSPECTION SUMMARY DUE DATE: August 30, 2013

I. BACKGROUND:

PSI-7977(sofosbuvir) is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed hepatitis C virus (HCV) replicon RNA replication in vitro and is intended for the treatment of chronic HCV infection. The applicant is seeking the following indication: the treatment of chronic hepatitis C (CHC) genotype 2 or 3 infection, in combination with peginterferon alfa and ribavirin (b) (4)

with or without ribavirin. The clinical studies supporting this program were conducted to support the pending application:

Protocols: Study P7977-1231 entitled “A Phase III, Multicenter, Randomized, Active-Controlled Study to Investigate the Safety and Efficacy of PSI-7977 and Ribavirin for 12 weeks Compared to Pegylated Interferon and Ribavirin for 24 weeks in Treatment Naïve Patients With Chronic Genotype 2 or 3 HCV Infection”(FISSION);

Study GS-US-334-0107 entitled “A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Weeks in Subjects With Chronic Genotype 2 or 3 HCV Infection who are Interferon Intolerant, Interferon Ineligible or Unwilling to Take Interferon ”(POSITRON) and

Study GS-US-334-0110 entitled “A Phase III, Open-Label Study to Investigate the Safety and Efficacy of GS-7977 With Peginterferon Alfa 2a and Ribavirin for 12 Weeks in Treatment-Naïve Subjects With Chronic Genotype 1, 4, 5 or 6 HCV Infection”(NEUTRINO).

Investigational Drug

HCV is a leading cause of liver disease worldwide and has become a focus of considerable medical research. More than 50% of HCV infections become chronic and may lead to the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma. Complications of liver disease due to HCV are the leading cause of liver failure requiring liver transplantation. Current therapies are based on peginterferon-alfa (PegIFN alpha) in combination with ribavirin (RBV). This combination yields a sustained virologic response in approximately 45% of treatment naïve subjects infected with genotype 1 (GT-1) HCV. In addition to the limited efficacy on genotype 1 HCV, this combination has significant side effects and is poorly tolerated in some subjects. The side effects include influenza-like symptoms, hematological abnormalities and neuropsychiatric symptoms.

Gilead Sciences, Inc has developed PSI-7977 (sofosbuvir), because of a need for new compounds that may overcome the disadvantages of current HCV therapy. Recent clinical studies have demonstrated the efficacy of direct acting antiviral drugs (DAA) in combination with PEG/RBV administered for 24-48 weeks in patients with chronic HCV GT-1. Although these regimens have demonstrated sustained viral response (SVR) rates which are superior to PEG/RBV alone in patients with HCV GT-1, they are not approved for treatment of patients

with HCV GT-2 or GT-3. This new investigational drug acting directly on the virally encoded protease target has demonstrated significant reduction in HCV ribonucleic acid (RNA) levels and improved SVR rates can be achieved when administered in combination with PegIFN alpha and RBV. The HCV-encoded NS5B protease is essential for viral replication and multidisciplinary discovery research has led to new specific and potent NS5B-directed hepatitis C virus replicon RNA replication. PSI-7977 is being developed as an oral formulation.

PSI-7977 (sofosbuvir) an NME, is currently being reviewed in support of an application for treatment of HCV infected naïve and relapsed subjects. Safety and efficacy in support of the application are based partially on 12-week data from PSI-7977-1231, a phase 3 trial comparing PSI7977 in combination with ribavirin vs pegylated interferon and ribavirin in treatment-naïve genotype (GT-2 or GT-3) HCV-infected subjects.

The Applicant-sponsored three studies were submitted in support of the application. This is a brief summary of the studies:

Protocol PSI-7977-1231

This protocol was a randomized, multicenter, active-controlled phase III study to investigate the safety and efficacy of PSI-7977 and ribavirin for 12 weeks compared to pegylated interferon and ribavirin. The study consisted of a screening period with a maximum duration of 6 weeks, a response-guided 12 (Arm A) or 24 (Arm B) week treatment period and a 48-week follow-up period. A target of 500 treatment-naïve subjects with documented chronic genotype 2 or 3 HCV infection, stratified for HCV genotype 2 or 3, baseline HCV RNA levels ($<6 \log_{10}$ IU/ml or $> 6 \log_{10}$ IU/ml), and presence of cirrhosis (present or absent), were randomized in a 1:1 ratio to one of two treatment arms:

- Arm A: 12 weeks of PSI-7977 400mg QD in combination with RBV
- Arm B: 24 weeks of PEG/RBV

Subjects with GT-2 and GT-3 were enrolled in approximately a 1:3 ratio. All subjects who had received at least one dose of study therapy were followed for 24 weeks after discontinuation of therapy to determine if SVR 24 has been achieved, or to determine the presence of any drug-resistant variants.

The objective of this study was to determine the efficacy of PSI-7977 in combination with RBV administered for 12 weeks compared with PEG/RBV administered for 24 weeks in treatment-naïve patients with HCV genotype 2 or 3 as assessed by the rate of sustained viral response (SVR) at week 12. SVR12 is HCV RNA $<$ lower limit of quantification (LOQ) 12 weeks after cessation of therapy.

The secondary objectives of this study were: 1) to assess the safety and tolerability of PSI-7977 administered for 12 weeks as measured by the frequency of deaths, serious adverse events, discontinuations due to adverse events, and grade 3 or 4 laboratory abnormalities, and 2) to describe rates of failure in the PSI-7977 treatment arm.

Protocol GS-US-334-0107

This protocol was a randomized, double-blind, multicenter, placebo-controlled study that examined the safety, tolerability, and antiviral efficacy of GS-7977 and ribavirin compared with GS-7977 placebo and RBV placebo in subjects with chronic GT-2 or GT-3 HCV infection who are IFN-intolerant, IFN ineligible or unwilling to take IFN. The study consisted of a screening period with a maximum duration of 6 weeks, a response-guided 12 or 24 week (GS-7977 treatment group) or 24-week post treatment period. The total time to complete all study visits was approximately 42 weeks. A target of 240 subjects were randomized in a 3:1 ratio to two treatment arms:

- Arm 1: GS-7977 400mg QD in combination with RBV (n=180)
- Arm 2: GS-7977 placebo 400mg QD + RBV placebo BID (n=60)

Randomization was stratified by the presence or absence of cirrhosis at screening. Approximately 20% of the subjects enrolled had evidence of cirrhosis at screening. HCV RNA results were blinded to the sponsor and investigator until the subject had completed the 4-week post-treatment assessments.

The objective of this study was to determine the efficacy of treatment with GS-7977+RBV compared with GS-7977 Placebo + RBV Placebo as measured by the rate of sustained viral response 12 weeks after Discontinuation of Therapy (SVR12) as shown below:

1) At the **actual end of treatment (EOT)**

- HCV RNA levels <25 IU/mL undetectable

AND

2) At the **time point of SVR12** (i.e., 12 weeks after the planned EOT)

- HCV RNA levels <25 IU/mL undetectable

OR

- HCV RNA levels <25 IU/mL detectable

The secondary objectives of this study were: 1) to determine the proportion of subjects who attain SVR at 4 and 24 weeks after treatment discontinuation of therapy (SVR4 and SVR 24), and 2) to evaluate the emergence of viral resistance to GS-7977 during treatment and after treatment discontinuation.

Protocol GS-US-334-0110

This protocol was a phase 3, multicenter, open-label study that evaluated the safety, tolerability and antiviral efficacy of GS-7977 with PEG and RBV in treatment naïve subjects with chronic genotype 1, 4, 5 or 6 HCV infection. The study consisted of a screening period with a maximum duration of 28 days, a response-guided 12 week (GS-7977 treatment group) or 24-week post treatment period. The total time to complete all study visits was approximately 40 weeks. A target of 300 subjects were treated for 12 weeks with GS-7977 (400mg QD) + PEG (189ug/week) + RBV (1000 or 1200 mg/day). Approximately 20% of the enrolled subjects had evidence of cirrhosis at screening.

The primary objectives of this study were: 1) to determine the efficacy of treatment with GS-7977+ PEG+RBV as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12), and 2) to evaluate the safety and tolerability of GS-7977 + PEG + RBV as assessed by review of accumulated safety data.

The secondary objectives of this study were; 1) to determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4and SVR 24), and 2) to evaluate the emergence of viral resistance to GS-7977 during treatment and after discontinuation of treatment.

The review division requested inspection of five clinical investigators for the pivotal protocols studies noted above because data from the protocols are considered essential to the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average, and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations. In addition, because of limited experience with this drug at foreign sites, it was decided to inspect foreign sites to verify the quality of conduct of the studies.

II. RESULTS (by protocol/site):

Name of CI, location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
Alessandra Mangia, M.D San Giovanni Rotondo Foggia, Italy 71013 Site #1235	Protocol P7977-1231 Number of subjects: 14	July 29 to August 1, 2013	Pending (preliminary classification NAI)
Victor Feinman, M.D. Mount Sinai Hospital 600 University Ave, Rm.1190, Toronto, Ontario Canada M5G 1X5 Site# 1252	Protocol P7977-1231 Number of subjects: 9	July 8 to 12, 2013	Pending (preliminary classification NAI)
K. Rajender Reddy, M.D. Hospital of the U. of Pennsylvania 3400 Spruce St. Philadelphia, PA 19104 Site# 2130	Protocol GS-US-334-0107 Number of subjects: 8	June 10 to14, ,2013	Pending (Preliminary classification NAI)
Giuseppe Morelli, M.D. University of Florida 1600 Southwest Archer Rd Gainesville, FL 32610 Site #4139	Protocol GS-US-334-0107 Number of subjects: 14	June 24 to 27, 2013	NAI

Name of CI, location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
Maribel Rodriguez-Torres, M.D 998 Munoz Rivera Ave San Juan, PR 00927 Site #4262	Protocol GS-US-334-0110 Number of subjects: 16	August 7 to 12, 2013	Pending (preliminary classification NAI)
Mitchell Davis, M.D. South Florida Central Gastroenterology, PA 1447 Medical Park Blvd, Suite 205 Wellington, FL 33414 Site#5498	Protocol GS-US-334-0110 Number of Subjects 17	June 13 to 21, 2013	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. Alessandra Mangia, M.D
Foggia, Italy 71013

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 204-671, Study Protocol P7977-1231. At this site, a total of 15 subjects were screened, one subject was reported as a screen failure, 14 subjects were randomized into the study, and 11 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 6 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Mangia. However, minor isolated cases of inaccuracies were noted and discussed with the clinical investigator. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to

the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.

- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Mangia's site are considered reliable and acceptable in support of the pending application.

2. Victor Feinman, M.D.
Canada, M5G 1X5

- a. **What Was Inspected:** This inspection was performed as a data audit for NDA 204-671, Study Protocol P7977-1231. At this site, a total of nine subjects were screened, and nine subjects were randomized into the study. Six (6) completed the study and three subjects were reported as virologic failures. Five subjects enrolled in Arm B-PEG/RBV continued into the Open Label Study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for nine subjects were reviewed for primary/secondary endpoints. The medical records/source documents for all subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Feinman. The medical records reviewed were found to be in order and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. **Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Feinman's site are considered reliable and may be used in support of the pending application.

3. K. Rajender Reddy, M.D.
Philadelphia, PA 19104

- a. **What Was Inspected:** This inspection was performed as a data audit for NDA 204-671 Study Protocol GS-US-334-0107. At this site, a total of ten subjects were screened, two subjects were reported as screen failures, eight (8) subjects were randomized into the study, and all eight completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed including drug accountability records, vital signs, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site. There were no known limitations to the inspection.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Reddy. Our investigation found incomplete documentation regarding the description of adverse events symptoms concerning a skin reaction, amount of redness and location where Subject 7335 experienced these symptoms, and whether the symptoms were resolved or ongoing.

The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events.

- c. Assessment of Data Integrity:** Although a minor regulatory deviation was noted, the finding is unlikely to affect integrity of the data as it appears to be an isolated incidence and not systemic in nature. The data from Dr. Reddy's site are considered reliable and appear acceptable in support of the pending application.

**4. Giuseppe Morelli, M.D.
Gainesville, FL 32610**

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 204-671, Study Protocol GS-US-334-0107. At this site, a total of 15 subjects were screened, one subject was reported as screen a failure, 14 subjects were randomized into the study, and 14 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 14 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Morelli. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.

- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Morelli’s site is considered reliable and acceptable in support of the pending application.

**5. Maribel Rodriguez-Torres, M.D.
San Juan, PR 00927**

- a. **What was Inspected:** This inspection was performed as a data audit for NDA 204-671 Study GS-US-334-0110. At this site, a total of 21 subjects were screened, five subjects were reported as screen failures, 16 subjects were randomized into the study, and 16 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment with the exception that the informed consent document for Subject 4262-6430 for the pharmacogenomics substudy was not fully signed and dated by the subject and the person obtaining consent.

The medical records/source documents for all subjects were reviewed for primary/secondary endpoints. The medical records for the majority of subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Rodriguez-Torres. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Rodriguez-Torres’s site is considered reliable and acceptable in support of the pending application.

**6. Mitchell Davis, M.D.
Wellington, FL 33414**

- a. **What was Inspected:** This inspection was performed as a data audit for NDA 204-671 Study GS-US-334-0110. At this site, a total 19 subjects were screened, two subjects were reported as screen failures, 17 subjects were randomized into the study, and 16 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed for primary/secondary endpoints. The medical records for the majority of subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings,

to include primary efficacy endpoints and adverse events. The field investigator selected five subjects and reviewed HCV-RNA viral loads by visits and found no discrepancies.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Davis. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Davis’s site is considered reliable and acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Six clinical investigator sites were inspected in support of this application. The inspection of the six clinical investigators listed above revealed no regulatory violations. The final classification for Dr. Morelli’s site is No Action Indicated (NAI) and the pending classification for the other five inspections is NAI. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Overall, the data submitted from these six sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
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Janice Pohlman, M.D. M.P.H. covering for
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Acting Branch Chief
Good Clinical Practice Assessment Branch

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

/s/

ANTOINE N EL HAGE
08/21/2013

SUSAN LEIBENHAUT
08/21/2013

JANICE K POHLMAN
08/21/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 204671
Application Type: New NDA (Type 1, NME) PDUFA V
Name of Drug: sofosbuvir, 400 mg tablets
Applicant: Gilead Sciences, Inc.
Submission Date: April 6, 2013
Receipt Date: April 8, 2013

1.0 Regulatory History and Applicant's Main Proposals

Gilead Sciences submitted a new drug application for sofosbuvir, 400 mg tablets. Gilead proposed the following indication “[TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults.”

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 21, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required

Selected Requirements of Prescribing Information (SRPI)

• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *Sponsor should remove the additional space between product title and Initial US Approval.*

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information (SRPI)

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: *Sponsor should add the established pharmacologic class to the indications and usage section of the HL*

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

Selected Requirements of Prescribing Information (SRPI)

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information (SRPI)

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

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

/s/

LINDA C ONAGA
06/06/2013

KAREN D WINESTOCK
06/07/2013

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 # 204671 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBN Established/Proper Name: sofosbuvir Dosage Form: tablet Strengths: 400 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: April 6, 2013 Date of Receipt: April 8, 2013 Date clock started after UN:		
PDUFA Goal Date: December 8, 2013		Action Goal Date (if different): December 6, 2013
Filing Date: June 7, 2013		Date of Filing Meeting: May 8, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): [TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<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>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input checked="" type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input 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 106739, IND 112681, IND 111572, IND 104522				
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>	X			
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>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
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>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input 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</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
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)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes, # years requested: 5 YEARS <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?		X		
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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

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

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<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?			X	
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)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
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)?	X			
<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?	X			
<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
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in 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...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
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>			X	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC notified PeRC date: August 14, 2013
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>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?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		X		
<p>Proprietary Name</p> <p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>		X		Sponsor submitted tradename request under IND. 4/3013 OSE RPM informed RPM that a denial letter would be sent to sponsor.
<p>REMS</p> <p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>			X	
<p>Prescription Labeling</p> <p>Check all types of labeling submitted.</p>	<input type="checkbox"/> Not applicable			
	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI)			

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

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

	<input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			Yes, submitted April18, 2013
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Yes, submitted April18, 2013
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Yes
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				

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

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)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): Clinical - June 5, 2012 CMC Only – October 11, 2011 Clinical – August 18, 2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 14, 2013	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): Two SPA Carcinogenicity agreement 11/3/2010				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 8, 2013

BLA/NDA/Supp #: 204671

PROPRIETARY NAME: TBN

ESTABLISHED/PROPER NAME: sofosbuvir

DOSAGE FORM/STRENGTH: 400 mg tablets

APPLICANT: Gilead Sciences, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): [TRADE-NAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults

BACKGROUND:

Gilead Sciences, Inc. (Gilead) submitted a new drug application (NDA) for sofosbuvir (GS-7977), a direct-acting antiviral agent for the treatment of chronic hepatitis C (CHC) infection. The application contains 4 phase 3 and additional phase 2 studies to support the following proposed indication and dosage and administration:

[TRADE-NAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults

	Duration	[TRADE-NAME] Dose (daily)	Peg-interferon Dose	Ribavirin Dose (daily)	
Treatment-naïve genotype 1, 4, 5, or 6	12 weeks	400 mg	See peg-interferon prescribing information	See ribavirin prescribing information	
Genotype 2	12 weeks		NA		<75 kg = 1000 mg ≥75 kg =1200 mg
Genotype 3	16 weeks				
Awaiting liver transplantation	Until liver transplantation				

Sofosbuvir is a new molecular entity and is subject to “The Program” under PDUFA V.

The application was received on April 8, 2013 and the PDUFA V goal date is December 8, 2013 (10 month, priority).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Linda C Onaga	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Sarah Connelly		Y
Clinical	Reviewer:	Poonam Mishra	Y
	TL:	Sarah Connelly	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lisa Naeger Eric Donaldson	Y
	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	Huimin (Jenny) Zheng	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Xiaojing Karen Qi	Y
	TL:	Wen Zeng	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Ellis	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	George Lunn Fuqiang Liu	Y
	TL:	Stephen Miller	Y

Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steve Donald	N
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Morgan Walker	Y
	TL:	Jamie Wilkins Parker	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	Tony El Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Quality Biopharmaceutics	Reviewer:	Minerva Hughes	Y
	TL:	Angelica Dorantes	N
Patient Labeling (DMPP)	Reviewer:	Karen Dowdy	Y
	TL:	Barbara Fuller	Y
OSE/DMEPA PM	Reviewer:	A. Danyal Chaudhry	Y
	TL:		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<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 NME NDA or original BLA , 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</i> 	<input checked="" type="checkbox"/> YES Date if known: October 25, 2013 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<i>disease</i>	
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input 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>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <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"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input 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 type="checkbox"/> Not Applicable</p> <p><input checked="" 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 OMPQ? <p>Comments:</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 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>

<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Edward Cox, MD, Director, OAP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 8, 2013</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 checked="" 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 OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<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 [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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

/s/

LINDA C ONAGA
06/06/2013

KAREN D WINESTOCK
06/07/2013