CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205834Orig1s007, s008, s009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205834 SUPPL #7, #8, #9 HFD #

Trade Name HARVONI

Generic Name ledipasvir/sofosbuvir fixed-dose tablet

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

Supplement 7: 505(b)(1) SE5 New patient population supplement
Supplement 8: 505(b)(1) SE5 New patient population supplement
Supplement 9: 505(b)(1) SE5 New patient population supplement

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(b) (4)

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. GS-US-337-0123 (SOLAR-1) (US)
2. GS-US-337-0124 (SOLAR-2) (international)

1. GS-US-337-0123 (SOLAR-1) (US). A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

2. GS-US-337-0124 (SOLAR-2) (international). A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. GS-US-337-0123 (SOLAR-1) (US). A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

2. GS-US-337-0124 (SOLAR-2) (international). A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # 115268	YES ☒	NO ☐ Explain:
Investigation #2		
IND #	YES ☐	NO ☐ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES ☐ Explain:	NO ☐ Explain:
Investigation #2	
YES ☒ Explain: In the application, Gilead certified that the non-IND study was conducted or sponsored by Gilead.	NO ☐ Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Christian P. Yoder, BSN, MPH
Title: Regulatory Project Manager
Date: February 12, 2016

Name of Office/Division Director signing form: Debra Birnkrant, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTIAN P YODER
02/12/2016

DEBRA B BIRNKRANT
02/12/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205834 BLA #	NDA Supplement # 7, 8 ,9 BLA Supplement #	If NDA, Efficacy Supplement Type: SE5 *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Harvoni Established/Proper Name: ledipasvir and sofosbuvir Dosage Form: tablet		Applicant: Gilead Sciences Agent for Applicant (if applicable):
RPM: Christian P. Yoder		DAVP

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is February 26, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain N/A	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☒ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date 2/12/16
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 2/8/16
• Original applicant-proposed labeling	☒ Included 8/26/15
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 2/8/16
• Original applicant-proposed labeling	☒ Included 8/26/15
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ PLR review 2/12/16 RPM label review 2/12/16 DMEPA: ☒ 11/6/15 DMPP/PLT (DRISK): ☒ 2/2/16 OPDP: ☒ 2/4/16 SEALD: None CSS: None Product Quality: None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	8/25/15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 2/12/16
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: N/A – None of criteria apply to the supplements	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	6/1/15
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	2/10/16
PMR/PMC Development Templates *(indicate total number)* One	2/12/16
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	1/27/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical Review, pages 14-15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☒ Pharmacovigilance Review 12/4/15 ☒ Drug Utilization Review 2/2/16
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ 1/4/16
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	1/27/16
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	2/9/16
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	1/27/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	1/29/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	9/25/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Included in Integrated Quality Assessment
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable Re-evaluation date: ☐ Withhold recommendation ☒ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done 2/12/16
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done N/A
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done 2/16/16

From: Yoder, Christian
To: "Prachi Shah"
Subject: NDA 205834 S7 S8 S9 draft label
Date: Thursday, February 04, 2016 12:35:00 PM
Attachments: NDA 205834 draft-labeling-text-stk 2-4-16.docx
NDA 205834 draft-labeling-text-stk 2-4-16.pdf

Hello Prachi,

Please see additional proposed labeling changes attached for Harvoni supplements 7, 8 and 9.

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label no later than noon EST, Monday, February 8, 2016.

Thanks,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883
Email: christian.yoder@fda.hhs.gov

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

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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/

CHRISTIAN P YODER
02/04/2016

From:	Yoder, Christian
To:	"Prachi Shah"
Subject:	NDA 205834 draft label
Date:	Wednesday, January 27, 2016 2:12:00 PM
Attachments:	NDA 205834 draft-labeling-text-stk 1-27-16.docx

Hello Prachi,

Please see additional proposed labeling changes attached for Harvoni supplements 7, 8 and 9.

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label no later than Monday, February 1, 2016.

Thanks,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883
Email: christian.yoder@fda.hhs.gov

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

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/s/

CHRISTIAN P YODER
01/27/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **January 20, 2016**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8, and 9 that were received on August 26, 2015. Please see the following clinical comment and respond by January 22, 2016.

The Division has determined that the data from the ongoing (b) (4) be submitted as a postmarketing commitment.

> Collect, analyze and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

Please propose the time schedule for the following milestones.

Final Protocol Submission:

Study Completion:

Final Report Submission:

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
01/20/2016

From: Yoder, Christian
To: "Prachi Shah"
Subject: NDA 205834 S7 S8 S9 proposed label changes
Date: Tuesday, January 12, 2016 10:28:00 AM
Attachments: sNDA 205834 draft-labeling-text-stk 1-12-16.docx
sNDA 205834 draft-labeling-text-stk 1-12-16.pdf
Virology Supportive Information for labelling 010616.pdf

Hello Prachi,

Happy New Year!

See proposed labeling changes attached for Harvoni supplements 7, 8 and 9. See also attached file with virology supporting information.

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label no later than Tuesday, January 19, 2016.

Thanks,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883
Email: christian.yoder@fda.hhs.gov

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/s/

CHRISTIAN P YODER
01/12/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **December 3, 2015**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8, and 9 that were received on August 26, 2015. Please see the following clinical comment and respond by December 14, 2015:

1. During our review, we noted that transient elevations in ALT/AST values meeting the criteria ALT or AST > 2x baseline value, or ALT/AST > 3 x post-baseline nadir value were observed in 11 cases. Even though, in these 11 cases, increase from baseline or from post-baseline nadir value was observed at a single timepoint and resolved with continued study treatment, an alternative etiology explaining the transient fluctuations was not identified. Of note, none of these cases had decompensated disease at baseline. In addition, one case of isolated direct bilirubin elevation at week 8 was observed in a subject who had CPT stage C liver disease at baseline. Separately, there were four cases in which drug induced liver injury (DILI) could not be excluded (including one case confounded by lamotrigine use where ALT/AST increase was observed at week 6 and led to treatment discontinuation) and one case with insufficient data to make an adequate assessment.

   Taken together, the findings raise concern for DILI. In the context of your proposed indication in the decompensated population, it is imperative that any potential risk of liver injury is thoroughly assessed and adequately addressed at this time. We acknowledge your assessment for the individual cases mentioned above. We are now requesting your interpretation and assessment of the collective findings based on the totality of evidence.

   It is important to communicate through labeling the necessary safety-related findings to health care providers, particularly findings of concern which are observed in clinical

trials. We are requesting feedback regarding the need for additional labeling to convey the overall clinical trial findings.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
12/03/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **December 2, 2015**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8, and 9 that were received on August 26, 2015. Please see the following clinical comments and respond by December 4, 2015:

1. With reference to the case narrative submitted for subject ID 7926-76605, please clarify the dates when study treatment was started relative to hepatic decompensation and portal hypertension events.

2. Please confirm the subject identification information for Transplant case A discussed at the 3rd IAC meeting on Page 2 of the meeting minutes.

3. Please provide brief narratives for the following subjects with ALT, or AST or direct bilirubin increases.
   5627-75328
   3910-76329
   4472-76377

4. Please provide brief narratives including pertinent cardiac history and concomitant medication information for the following subjects with reported heart rate less than 50 bpm:
   7391-75376
   0676-76410
   1759-76212
   4472-76305

5. Please provide case narratives including serum creatinine values over time and concomitant medications for two renal events of interest: ID 0467-76344 and 7391-75377

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

_____

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
12/02/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **December 2, 2015**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8 and 9, that was received on August 26, 2015. Please see the following comment, and kindly respond as soon as possible, but no later than December 16, 2015:

1. Please submit sensitivity analyses for the primary efficacy endpoint SVR 12 excluding subjects enrolled from sites where the principal investigator and/or sub-investigators received significant payments or held significant equity interest as defined in 21 CFR 54.2. Submit a similar analysis for treatment-emergent adverse events, and drug-related adverse events. Provide the rationale for concluding a lack of substantial bias on part of the investigators as a result of significant financial arrangements.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
12/02/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **November 30, 2015**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8 and 9 that were received on August 26, 2015. Please see the following comments regarding the SOLAR studies and respond by December 7, 2015:

1. For some subjects, in both SOLAR studies, the baseline CPT score does not match the group assigned. Please explain the reason.

    - In SOLAR 1, there are 25 subjects for whom CPT category does not match the group assigned. Two of these subjects are amongst the 20 subjects for whom Trt01A was different from Trt01P. The list of these 25 subjects is listed below:

	USUBJID	TRT01A	TRT01P	FASFL	SVR12	Bcpt	Bmeld
1	GS-US-337-0123-5627-75126	Cohort A, Group 1 - 12 Weeks of Treatment	Cohort A, Group 1 - 12 Weeks of Treatment	Y	N	10	13
2	GS-US-337-0123-1516-75202	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	N	9	19
3	GS-US-337-0123-2738-75251	Cohort A, Group 2 - 24 Weeks of Treatment	Cohort A, Group 2 - 24 Weeks of Treatment	Y	N	9	17
4	GS-US-337-0123-0451-75523	Cohort B, Group 5 - 12 Weeks of Treatment	Cohort B, Group 5 - 12 Weeks of Treatment	Y	N	10	21
5	GS-US-337-0123-1516-75527	Cohort B, Group 5 - 24 Weeks of Treatment	Cohort B, Group 5 - 24 Weeks of Treatment	Y	N	5	7
6	GS-US-337-0123-0526-75107	Cohort A, Group 1 - 24 Weeks of Treatment	Cohort A, Group 1 - 24 Weeks of Treatment	Y	Y	6	13
7	GS-US-337-0123-0619-75151	Cohort A, Group 1 - 24 Weeks of Treatment	Cohort A, Group 1 - 24 Weeks of Treatment	Y	Y	10	11
8	GS-US-337-0123-6927-75150	Cohort A, Group 1 - 12 Weeks of Treatment	Cohort A, Group 1 - 12 Weeks of Treatment	Y	Y	10	11
9	GS-US-337-0123-7275-75145	Cohort A, Group 1 - 12 Weeks of Treatment	Cohort A, Group 1 - 12 Weeks of Treatment	Y	Y	10	16
10	GS-US-337-0123-0519-75223	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	13
11	GS-US-337-0123-0585-75154	Cohort A, Group 2 - 24 Weeks of Treatment	Cohort A, Group 1 - 24 Weeks of Treatment	Y	Y	9	15
12	GS-US-337-0123-1039-75602	Cohort A, Group 2 - 24 Weeks of Treatment	Cohort B, Group 6 - 24 Weeks of Treatment	Y	Y	9	14
13	GS-US-337-0123-5627-75220	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	14
14	GS-US-337-0123-5969-75225	Cohort A, Group 2 - 24 Weeks of Treatment	Cohort A, Group 2 - 24 Weeks of Treatment	Y	Y	9	15
15	GS-US-337-0123-6991-75210	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	8	15
16	GS-US-337-0123-8429-75226	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	11
17	GS-US-337-0123-1086-75420	Cohort B, Group 4 - 12 Weeks of Treatment	Cohort B, Group 4 - 12 Weeks of Treatment	Y	Y	7	9
18	GS-US-337-0123-1516-75427	Cohort B, Group 4 - 24 Weeks of Treatment	Cohort B, Group 4 - 24 Weeks of Treatment	Y	Y	7	10
19	GS-US-337-0123-8224-75424	Cohort B, Group 4 - 24 Weeks of Treatment	Cohort B, Group 4 - 24 Weeks of Treatment	Y	Y	7	11
20	GS-US-337-0123-8430-75435	Cohort B, Group 4 - 24 Weeks of Treatment	Cohort B, Group 4 - 24 Weeks of Treatment	Y	Y	7	20
21	GS-US-337-0123-0526-75501	Cohort B, Group 5 - 12 Weeks of Treatment	Cohort B, Group 5 - 12 Weeks of Treatment	Y	Y	10	23
22	GS-US-337-0123-1249-75505	Cohort B, Group 5 - 24 Weeks of Treatment	Cohort B, Group 5 - 24 Weeks of Treatment	Y	Y	6	15
23	GS-US-337-0123-0200-75607	Cohort B, Group 6 - 12 Weeks of Treatment	Cohort B, Group 6 - 12 Weeks of Treatment	Y	Y	9	12
24	GS-US-337-0123-0585-75604	Cohort B, Group 6 - 12 Weeks of Treatment	Cohort B, Group 6 - 12 Weeks of Treatment	Y	Y	9	8
25	GS-US-337-0123-4969-75605	Cohort B, Group 6 - 24 Weeks of Treatment	Cohort B, Group 6 - 24 Weeks of Treatment	Y	Y	9	21

- In SOLAR 2, there are 19 subjects for whom CPT category does not match the group assigned. Five of them were amongst the 19 subjects for whom Trt01A was different from Trt01P. The list of these 19 subjects is listed below.

	USUBJID	TRT01A	TRT01P	FASFL	SVR12	Bcpt	Bmeld
1	GS-US-337-0124-0452-76215	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y		9	11
2	GS-US-337-0124-1069-76202	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	N	9	14
3	GS-US-337-0124-2456-76238	Cohort A, Group 1 - 24 Weeks of Treatment	Cohort A, Group 2 - 24 Weeks of Treatment	Y	Y	11	14
4	GS-US-337-0124-7926-76150	Cohort A, Group 1 - 12 Weeks of Treatment	Cohort A, Group 1 - 12 Weeks of Treatment	Y	Y	10	16
5	GS-US-337-0124-0454-76231	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	11
6	GS-US-337-0124-0465-76249	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	11
7	GS-US-337-0124-0477-76230	Cohort A, Group 2 - 24 Weeks of Treatment	Cohort A, Group 2 - 24 Weeks of Treatment	Y	Y	9	14
8	GS-US-337-0124-1036-76210	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	14
9	GS-US-337-0124-1305-76115	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 1 - 12 Weeks of Treatment	Y	Y	9	15
10	GS-US-337-0124-6437-76222	Cohort A, Group 2 - 12 Weeks of Treatment	Cohort A, Group 2 - 12 Weeks of Treatment	Y	Y	9	12
11	GS-US-337-0124-0557-76439	Cohort B, Group 4 - 12 Weeks of Treatment	Cohort B, Group 4 - 12 Weeks of Treatment	Y	Y	7	6
12	GS-US-337-0124-0454-76540	Cohort B, Group 5 - 12 Weeks of Treatment	Cohort B, Group 5 - 12 Weeks of Treatment	Y	Y	5	13
13	GS-US-337-0124-0465-76516	Cohort B, Group 5 - 24 Weeks of Treatment	Cohort B, Group 5 - 24 Weeks of Treatment	Y	Y	6	12
14	GS-US-337-0124-1043-76408	Cohort B, Group 5 - 12 Weeks of Treatment	Cohort B, Group 4 - 12 Weeks of Treatment	Y	Y	6	9
15	GS-US-337-0124-1088-76539	Cohort B, Group 5 - 12 Weeks of Treatment	Cohort B, Group 5 - 12 Weeks of Treatment	Y	Y	6	11
16	GS-US-337-0124-1474-76519	Cohort B, Group 5 - 24 Weeks of Treatment	Cohort B, Group 5 - 24 Weeks of Treatment	Y	Y	10	19
17	GS-US-337-0124-3922-76526	Cohort B, Group 5 - 24 Weeks of Treatment	Cohort B, Group 5 - 24 Weeks of Treatment	Y	Y	6	11
18	GS-US-337-0124-7926-76605	Cohort B, Group 5 - 24 Weeks of Treatment	Cohort B, Group 6 - 24 Weeks of Treatment	Y	Y	11	18
19	GS-US-337-0124-0480-76534	Cohort B, Group 6 - 24 Weeks of Treatment	Cohort B, Group 5 - 24 Weeks of Treatment	Y	Y	9	13

2. One subject (GU-US-337-0124-7926-76522) was assigned in group 5, which is the post-transplant cohort, and had liver transplantation during the study. Please clarify.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
11/30/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **November 10, 2015**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8 and 9, that was received on August 26, 2015. Please see the following comment, and respond by November 13, 2015:

1. Please submit the ADLB dataset for SOLAR-1. If this has been submitted in the sNDA, please provide us with the location.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
11/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205834/S-7
NDA 205834/S-8
NDA 205834/S-9

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your supplemental New Drug Applications (sNDA) dated August 26, 2015, received August 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Harvoni® (ledipasvir and sofosbuvir), fixed-dose combination tablet 90 mg/400 mg.

We also refer to your amendments dated September 2, 2015 and September 14, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 26, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 3, 2016.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. The subsection heading of Section 14.4 in the Table of Contents does not match the subsection heading in the FPI: "…Decompensated Liver Disease" vs. "…Decompensated Cirrhosis."

2. The horizontal line separating the Table of Contents from the Full Prescribing Information is missing.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 9, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above request for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list

each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
10/21/2015

From: Winestock, Karen
To: "Prachi Shah"; Mani, Nina
Cc: Yoder, Christian
Subject: RE: Harvoni SOLAR sNDAs - Mid-Cyle Meeting and Filing Letter
Date: Tuesday, October 13, 2015 12:59:00 PM

Hello Prachi,

At this time, the review team has not discussed scheduling a post-midcycle telecon.

If the Agency grants your application(s) a priority review, a letter will be sent to you on or before the 60-day filing date, which is October 25, 2015. If a standard review is granted, you will receive a letter by day 74.

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500

From: Prachi Shah [mailto:Prachi.Shah@gilead.com]
Sent: Sunday, October 11, 2015 3:07 PM
To: Winestock, Karen; Mani, Nina
Cc: Yoder, Christian
Subject: FW: Harvoni SOLAR sNDAs - Mid-Cyle Meeting and Filing Letter

Dear Nina and Karen,

I am the Gilead regulatory contact for IND 115268 and NDA 205834 and I am reaching out to you as I received an out of office message for Christian. Would either of you kindly provide a response to my questions below regarding Harvoni SOLAR Supplements S007-S009?

Thank you,
Prachi

From: Prachi Shah
Sent: Sunday, October 11, 2015 11:34 AM
To: Yoder, Christian (Christian.Yoder@fda.hhs.gov)
Subject: Harvoni SOLAR sNDAs - Mid-Cyle Meeting and Filing Letter

Dear Christian,

Reference is made to the Harvoni SOLAR sNDAs (NDA 205834; S/007-009) submitted on 26 Aug

2015. I am checking to see if Gilead should expect a Mid-Cycle meeting for these supplements. We had a Mid-Cycle meeting for the supplements submitted in May and therefore, I am checking to see if we should expect one for these supplements as well?

Additionally, can you please let me know when we can expect the filing letter/Priority review determination for these supplements?

Thank you,
Prachi

Prachi Shah, MBS, RAC
Manager | Regulatory Affairs
Gilead Sciences, Inc. | 333 Lakeside Dr. | Foster City, CA 94404
☎: 650.522.2308 | 🖷: 650.522.5489 | Prachi.Shah@gilead.com

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/s/

KAREN D WINESTOCK
10/13/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **205834, Supplements 7, 8, and 9**

Drug: **Harvoni (ledipasvir and sofosbuvir)**

Date: **September 10, 2015**

To: **Ms. Prachi Shah, Associate Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 205834 Information request**

Please refer to your New Drug Application 205834, Supplements 7, 8 and 9, that was received on August 26, 2015. Please see the following clinical comment, and respond by September 15:

1. Please explain the difference between the categories, Interim, Interim 2, Interim 2 Amendment 1 in module 5.3.5.1 and clarify why these categories are not present under 5.3.5.2. If the categories are explained in detail in the sNDA, please provide us with the location.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
09/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205834/S-7
NDA 205834/S-8
NDA 205834/S-9

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

We have received your supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 205834

SUPPLEMENT NUMBERS: 7, 8, and 9

PRODUCT NAME: Harvoni® (ledipasvir and sofosbuvir), fixed-dose combination tablet, 90 mg/400 mg

DATE OF SUBMISSION: August 26, 2015

DATE OF RECEIPT: August 26, 2015

These supplemental applications propose the following changes:

NDA 205834/S-7

- To expand the patient population to include subjects with genotype 1, chronic hepatitis C virus infection who are liver transplant recipients

NDA 205834/S-8

- To expand the patient population to include subjects with genotype 4, chronic hepatitis C virus infection who are liver transplant recipients

NDA 205834/S-9

- To expand the patient population to include subjects with decompensated cirrhosis who have genotype 1, chronic hepatitis C virus infection.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 25, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
09/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115268

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Associate Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HARVONI® (ledipasvir/sofosbuvir) fixed dose combination tablet.

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2015. The purpose of the meeting was to discuss a supplemental NDA submission containing data from the SOLAR-1 and SOLAR-2 clinical development programs.

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

If you have any questions, call Linda C. Onaga, MPH, Senior Regulatory Project Manager at (301) 796-0759 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sNDA

Meeting Date and Time: May 1, 2015
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: 115268
Product Name: Harvoni® (ledipasvir/sofosbuvir) fixed dose combination tablet
Indication: treatment of chronic genotype 1 hepatitis C infection

Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Linda Onaga, MPH

FDA ATTENDEES

1. Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
2. Jeff Murray, MD, MPH, Deputy Director, DAVP
3. Poonam Mishra, MD, MPH, CDTL, Deputy Director of Safety, DAVP
4. Kim Struble, PharmD, Clinical Team Lead, DAVP
5. Adam Sherwat, MD, Clinical Team Lead, DAVP
6. Russ Fleisher, MD, Acting Clinical Team Lead, DAVP
7. Mary Singer, MD, Clinical Team Lead, DAVP
8. Charu Mullick, MD, Clinical Reviewer, DAVP
9. Sarah Connelly, MD, Clinical Reviewer, DAVP
10. Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
11. Shirley Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP)
12. Fang Li, PhD, Pharmacometrics Reviewer, OCP
13. Greg Soon, PhD, Biometrics Team Lead, Division of Biometrics IV (DBIV)
14. Antonie El Hage, PhD, Division of Scientific Inspections (DSI)
15. Mammah Borbor, MBA, MS, Regulatory Project Manager, DAVP
16. Garrette Marti-Yeboah, PharmD, Regulatory Project Manager, DAVP
17. Karen Winestock, Chief, Project Management Staff, DAVP
18. Linda Onaga, MPH, Senior Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

Gilead Attendees:

1. John McHutchison, MD, Executive Vice President, Liver Diseases
2. Mani Subramanian, MD, PhD, Vice President, Clinical Research, Liver Diseases
3. Diana Brainard, MD, Vice President, Clinical Research, Liver Diseases
4. Michele Anderson, Director, Regulatory Affairs
5. Ming Lin, PhD, Associate Director, Biostatistics
6. Prachi Shah, MBS, RAC, Associate Manager, Regulatory Affairs

External Attendees (Independent Adjudication Committee):

(b) (4)

1.0 BACKGROUND

HARVONI (ledipasvir/sofosbuvir) fixed dose combination tablet is approved for the treatment of chronic hepatitis C virus (HCV), genotype 1 infection. Gilead intends to submit a supplemental new drug application (sNDA) for HARVONI to update labeling with data from the SOLAR-1 and SOLAR-2 clinical development programs. SOLAR-1 (GS-US-334-0123) and SOLAR-2 (GS-US-334-0124) are phase 2, multicenter, open-label studies to investigate the safety and efficacy of HARVONI plus ribavirin administered either 12 or 24 weeks, in patients with chronic HCV who have advanced liver disease or who are post liver transplant. SOLAR-1 was conducted in the United States, while SOLAR-2 was conducted in the European Union, Canada, Australia, and New Zealand.

Gilead requested a type B Pre-sNDA meeting with the Division of Antiviral Products to discuss key aspects related to the sNDA submission strategy, proposed indication, content and format of the application, and approach for the NDA safety update. Gilead expects to submit a sNDA for LDV/SOF FDC third quarter 2015.

The objectives of this meeting are:

1. To seek agreement with the Agency on a strategy by which to assess the liver safety of HARVONI in subjects with decompensated cirrhosis, including, but not limited to, laboratory cutoffs by which to screen for drug induced liver injury (DILI)

2. To seek comments and agreement from the Agency on the scope, of the SOLAR sNDA, which will include information from Study GS-US-334-0123 (SOLAR-1) and GS-US-334-0124 (SOLAR-2)

3. To seek comment and agreement on the SOLAR sNDA

FDA sent Preliminary Comments to Gilead Sciences, Inc. on Monday April 27, 2015.

2.0 DISCUSSION

Gilead agreed with the Agency's responses in the April 27, 2015 Preliminary Comments. Gilead requested that this meeting focus on the attached slide presentation.

2.1 IAC Responsibilities (Slide 5)

Discussion:

Based on the FDA's Preliminary Reponses to Question 1, the criteria for case selection in decompensated cirrhotic populations will also include ALT or AST greater than three times nadir or greater than two times baseline. The Independent Adjudication Committee (IAC) will also review fatal events, discontinuations due to hepatic events or hepatic stopping criteria and cases requiring transplantation. For the selected cases, adjudication will occur in 3 ways: unlikely to be related to study drug, study drug cannot be ruled out as an etiologic agent, and insufficient information to make a determination. DAVP asked Gilead to provide the rationale in the sNDA for deviating from the causality assessment criteria used by the Drug-Induced Liver Injury Network (DILIN). Lastly, the IAC will discuss and provide their own assessment of the clinical significance of Model for End Stage Liver Disease (MELD)/Child Pugh Turcotte (CPT) scores for labeling considerations.

2.2 IAC Meetings (Slide 6)

Discussion:

The IAC met on March 3, 2015 to discuss proposed laboratory cutoffs by which to screen for drug induced liver injury (DILI), and met on March 20, 2015 to adjudicate cases for direct bilirubin elevations and serious adverse events of hepatic failure, and discussed how the data should be displayed in labeling. Each IAC member reviews each case independently and forwards their assessment to the IAC Chair. The IAC then meets as a group to discuss their independent assessment of the cases and reach a consensus for each case through group decision. There was some discordance amongst the IAC members, which merited additional discussions, but eventually the committee came to an agreement.

Dr. (b) (4) commented on the impossibility of attributing a definite causal relationship between the drug and the event. For patients with Child Pugh Class B or C, many things can precipitate a change in liver function and/or hepatic failure. Dr. (b) (4) provided some statistics from the United Network for Organ Sharing (UNOS) and the Scientific Registry of Transplant Recipients

(SRTR) databases. These data provide a natural history of liver disease progression for patients with decompensated liver disease and those listed for liver transplantation. FDA requested these data are included in the sNDA to provide context for the trial results.

During the adjudication for bilirubin and serious adverse events, most of the cases were characterized into two groups, unlikely to be related to study drug, or study drug cannot be ruled out as an etiologic agent. Of the cases that were adjudicated, one case had insufficient information to make a causality determination. This subject had travelled to Europe and died while on travel; very little was known about his health status prior to his death.

2.3 SOLAR-1/2 Preliminary Integrated Safety Data (Slide 8)

Discussion:

Gilead provided a brief overview of the preliminary integrated SOLAR-1 and SOLAR-2 data. This analysis will include data in all subjects through the last patient dose.

2.4 SOLAR-1/2 Preliminary Integrated Safety Data Study Design (Slide 9)

Discussion:

Slide 9 is the schematic of how Gilead intends to group the study data for analysis.

2.5 SOLAR-1/2 Preliminary Integrated Safety Data Study Baseline Liver Disease Characteristics (Slides 10, 11)

Discussion:

Gilead presented the baseline liver disease characteristics from subjects in SOLAR-1 and SOLAR-2. The clinical utility of MELD and CPT scores was discussed. Experts agreed that the average MELD scores at the time of liver transplant in the U.S. varied by region. The IAC concluded that both the MELD and CPT scores were important for labeling. The committee will review data and create MELD plots that will be submitted with the sNDA.

2.6 SOLAR-1/2 Preliminary Integrated Safety Data Overall Safety Summary (Slides 12, 13)

Discussion:

Slide 12 focused on the overall safety summary of SOLAR-1 and SOLAR-2. Grade 3 or 4 adverse events were higher than what was seen in the (b) (4) clinical development program. However, the rates of adverse events leading to discontinuation of HARVONI were low. The deaths observed in these clinical trials will be adjudicated and analyzed. Seven transplants occurred during the treatment period and four additional transplants occurred within 30 days after completing treatment. The Division requested that the specific reasons for transplantation, outcomes, and other pertinent information should be included in the sNDA. The IAC will

discuss cases once adjudicated and provide Gilead with their final conclusions, which will be included in the sNDA submission.

2.7 SOLAR-1/2 Preliminary Integrated Safety Data Study Treatment-Emergent Deaths (Slide 14)

Discussion:

In SOLAR-1 and SOLAR-2 there were a total of 20 on-treatment deaths. Many of the deaths were due to some type of infection and/or liver failure. The data presented will be adjudicated and reviewed by the IAC for comments and conclusions.

2.8 MELD Score Cut-Offs (Slides 16, 17)

Discussion:

Gilead presented information on the MELD score cut-offs and the categories used to define the outcomes. For subjects with decompensated disease who achieve SVR12, MELD and CPT scores at 12 week post -treatment will be grouped into three categories: 1) no change, 2) improvement in score, and 3) worsening in score compared to baseline values. Gilead will compare a subject's baseline values to their post-treatment week 12 values. Gilead will create shift tables that classifies subjects with available MELD data according to greater than or equal to 15 or less than 15 at baseline and at post-treatment week 12 and for CPT classification at the same time points. The shift table is a representation of what is seen in clinical practice. A small change in clinical or laboratory parameters could increase a patient's MELD or CPT score. There were no differences observed between pre- and post-transplant subjects. The Division requested a summary of the Scientific Registry of Transplant Recipients (SRTR) database and the IAC safety assessment to be submitted with sNDA submission.

The IAC members and Gilead agreed that both MELD and CPT scores are clinically important (b) (4).

Subjects enrolled in SOLAR-1 and SOLAR-2 will be followed for 5 years. The IAC members stated that 5 years is more than enough time to evaluate effect on mortality. One year follow-up data would also provide a significant amount of information about patient outcomes post-treatment. Gilead stated willingness to follow patients for periods greater than five years if there are noticeable differences in outcomes that warrant continuation, if necessary. Gilead will provide their recommendations for monitoring this patient population in the sNDA submission.

IAC members agreed to create a Kaplan-Meier survival graph for patients over time and provide additional information on survival rates in the trial. Gilead will include this information in the sNDA submission.

2.9 Proposed Groups for Subgroup Analysis (Slides 19)

Gilead proposed to pool subjects into groups with and without decompensated cirrhosis. This will make the analysis more sensitive to detect differences. The Division requested Gilead submit both pooled analysis and safety by each trial arm individually for the sNDA submission; the sponsor agreed to submit both types of analyses

Regarding toxicity monitoring during the treatment period, the IAC members recommend monitoring based on the AASLD guidelines. Decompensated pre- and post-transplant patients are a unique population that requires frequent monitoring of bilirubin throughout the duration of treatment. Experts agreed that regardless of ribavirin use, direct bilirubin is an appropriate parameter for monitoring during treatment for potential DILI. It was also recommended that the stopping treatment should follow the current recommendations described in the approved HARVONI label.

If available, Gilead will provide available data for fatal events and serious hepatic events from observational cohorts or real world databases such as TRIO and HCV-TARGET. This data will be included in the Safety Update for sNDA.

Gilead plans to submit the sNDA by August 28, 2015.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

5.0 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

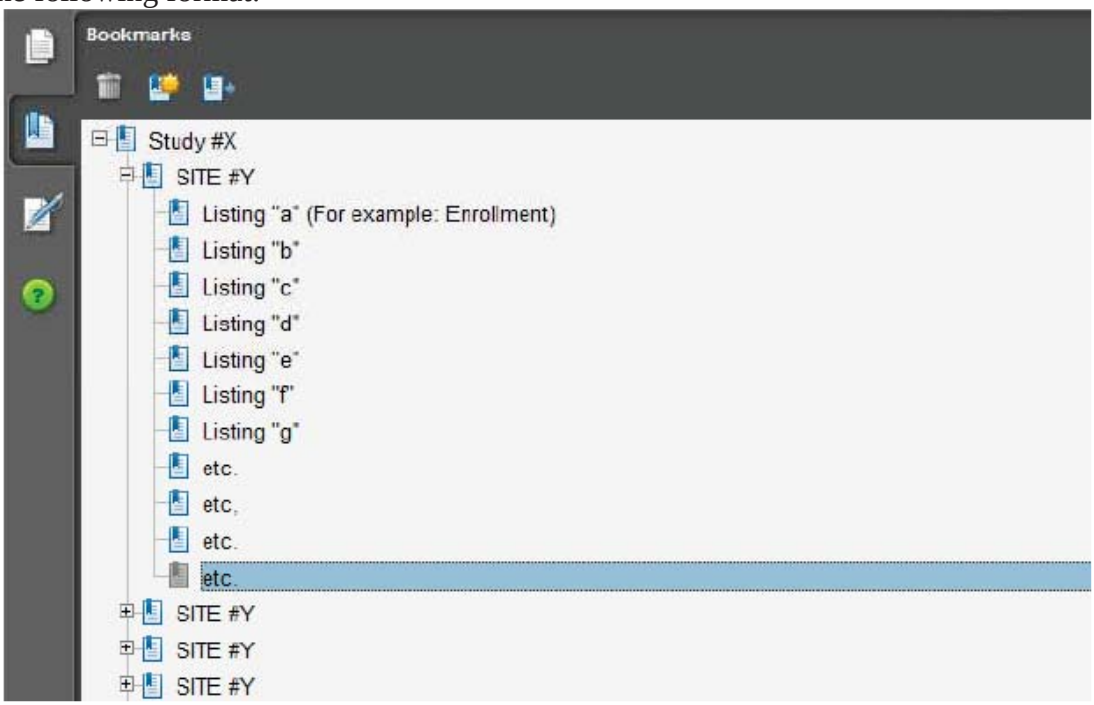
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

6.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

7.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Gilead will provide all IAC minutes.	Gilead	With sNDA submission
The IAC will review data and create MELD plots that will be submitted with the sNDA.	Gilead	With sNDA submission
The Division requested the reason for liver transplantation for all subjects who had a transplant during the trial, if available	Gilead	With sNDA submission
The Division requested a summary of the Scientific Registry of Transplant Recipients (SRTR) database and the IAC safety assessment to be submitted with sNDA submission.	Gilead	With sNDA submission
The Division requested Gilead submit with the sNDA their rationale for not using the DILIN criteria	Gilead	With sNDA submission
Gilead will provide their rationale and recommendations for labeling with regards to	Gilead	With sNDA submission

CPT and MELD changes or cut-offs and safety monitoring this patient population in the sNDA submission.		
IAC members agreed to create a Kaplan Myer survival table and provide additional information on survival rate information.	Gilead	With sNDA submission
The Division requested Gilead perform both unpooled and pooled analysis for the sNDA submission.	Gilead	With sNDA submission
Gilead will provide their rationale in writing for Division comments prior to the NDA including high level safety information from TARGET and TRIO.	Gilead	Prior to sNDA submission to allow for Division feedback

8.0 ATTACHMENTS AND HANDOUTS

Attached is the slide set presented by Gilead at this meeting.

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/s/

DEBRA B BIRNKRANT
06/01/2015