RESPONSE TO PREA NON-COMPLIANCE LETTER
SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Regulatory Operations
Division of Regulatory Operations for Infectious Diseases
Antivirals Group
Attention: London Harrison, MBEE, Regulatory Health Project Manager
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **NDA 205834 for Harvoni® (Ledipasvir/Sofosbuvir) Oral Tablets - Sequence 0273**
Response to FDA PREA Non-Compliance Letters (PMR 2780-2)
Prior Approval Supplement: Updated Labeling Study GS-US-334-1113

Dear Ms. Harrison:

Reference is made to NDA 205834 for Harvoni® (ledipasvir/sofosbuvir) oral tablets for treatment of hepatitis C virus (HCV) infection. Reference is also made to FDA letters regarding Harvoni NDA 205834 dated 22 May 2024: Notification of Non-Compliance with PREA (Reference ID: 5385423) and Information Request/Advice: Additional Comments on Non-Compliance Letters (Reference ID: 5385750). Both letters pertain to the postmarketing requirement (PMR) 2780-2 described below:

PMR 2780-2: Collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.

Gilead Sciences, Inc. (Gilead) hereby submits a response to the above referenced PREA Non-Compliance letter regarding PMR 2780-2 and affirms Gilead's continued commitment to fulfill all PMRs.

Clinical Study GS-US-334-1113 titled "*A Long Term Follow-up Registry for Adolescent and Pediatric Subjects Who Received a Gilead Hepatitis C Virus Direct Acting Antiviral (DAA) in Gilead-Sponsored Chronic Hepatitis C Infection Trials,*" collected at least 3 years of follow-up safety data to characterize long-term safety of Harvoni in pediatric subjects. This study was completed on 08 January 2023.

On 28 June 2023, Gilead submitted GS-US-334-1113 final Clinical Study Report (CSR) to NDA 205834 (Seq 0267). This submission was intended to complete fulfillment of PMR 2780-2 and was submitted 2 months before PMR deadline of 31 August 2023. In the CSR submission, Gilead indicated there were no proposed labeling changes based on the study results.

Following receipt of the PREA Non-Compliance letters, Gilead understands the Agency's position to provide a Prior Approval Supplement (PAS) with proposed labeling changes based on data derived from clinical study GS-US-334-1113.

As such, Gilead hereby submits proposed labeling changes as a PAS for Harvoni oral tablets, containing changes based on data derived from clinical study GS-US-334-1113. This PAS is prepared in Common Technical Document (CTD) format and includes draft labeling text with proposed labeling updates in Module 1.14.1, and Module 2.5 Clinical Overview. The final CSR and associated datasets were previously provided on 28 June 2023 (Seq 0267). This submission will also address outstanding items to complete fulfillment of PMR 2780-2. Additionally, a PAS containing proposed labeling changes for Harvoni oral pellets has also been submitted concurrently to NDA 212477 (Seq 0052).

Of note, Study GS-US-334-1113 was conducted under IND 106739 and therefore all other submissions associated with this study may be found in the aforementioned IND application. A letter cross referencing this submission has also been submitted to this IND (Seq 0602).

Please contact me at 253-951-1473 or jay.malmo1@gilead.com, if you have any questions or need additional information. You may also contact John Lombardo, Associate Director, Regulatory Affairs, at 650-522-5204 or john.lombardo2@gilead.com.

Sincerely,

[See appended electronic signature]

Jay Malmo
Contractor, Regulatory Affairs

CL Resp HVN PREA NC Rec 22May2024_ NDA 205834

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Jay Malmo1	Regulatory Affairs eSigned	26-Jun-2024 20:19:54