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RESEARCH**

*APPLICATION NUMBER:*

**205123Orig1s000**

**OTHER REVIEW(S)**

## 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.

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NDA 205123  
Product Name: simeprevir

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

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PMR/PMC Schedule Milestones: Final Protocol Submission: 05/31/2018  
Trial Completion: 07/31/2021  
Final Report Submission: 12/31/2021  
Other: \_\_\_\_\_ MM/DD/YYYY

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

Treatment for pediatric chronic hepatitis C patients 3 through 17 years of age

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.”

This is one of the trials that will be used to fulfill PREA requirements. The goal of the trial is to evaluate pharmacokinetics, safety and antiviral activity of simeprevir as a component of a combination antiviral treatment regimen in pediatric patients (3 to 17 years old) with chronic hepatitis C .

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.

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

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**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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VICTORIA L TYSON  
11/20/2013

## 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.

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NDA 205123  
Product Name: simeprevir

PMR Description: Collect long-term safety data for subjects enrolled in the pediatric simeprevir safety, pharmacokinetics and efficacy trial. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of simeprevir in pediatric subjects, including growth assessment, sexual maturation and characterization of simeprevir resistance-associated substitutions in viral isolates from subjects failing therapy.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/31/2019</u>
	Trial Completion:	<u>07/31/2024</u>
	Final Report Submission:	<u>01/31/2025</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

Long-term safety data in pediatric subjects treated in the simeprevir safety, pharmacokinetics and efficacy trial.

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.”

This is one of the trials that will be used to fulfill PREA requirements.

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.

Pediatric subjects 3 through 17 years of age

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

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**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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VICTORIA L TYSON  
11/22/2013

## 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.

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NDA# 205123  
Product Name: simeprevir

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PMR Description: Submit the final study report and datasets from the ongoing clinical trial TMC435HPC3005, entitled “A Phase 3, Randomized, Double-Blind, Double Dummy, Placebo-Controlled Study Conducted in the Asia-Pacific Region to Investigate the Efficacy, Pharmacokinetics, Safety and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon alfa-2a and Ribavirin in Treatment-naïve, Genotype 1 Hepatitis C-Infected Subjects.”

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PMR/PMC Schedule Milestones:	Trial Completion:	<u>02/28/2015</u>
	Final Report Submission:	<u>7/31/2015</u>

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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

Existing clinical data indicate that simeprevir exposures are higher in people with East Asian ancestry compared to those without East Asian ancestry due to physiological characteristics (e.g. lower hepatic levels of the metabolizing enzyme CYP3A). In Phase 1 studies, mean simeprevir exposures (AUC) were 2- to 3-fold higher in healthy subjects of East Asian descent compared to healthy Caucasian subjects. In Phase 3 studies evaluating simeprevir 150 mg QD, mean simeprevir exposures were 3.4-fold higher in HCV-infected patients of East Asian descent compared to the pooled Phase 3 population. However, the number of East Asian patients evaluated in the Phase 3 trials was very small (n=15, 1.9%) and the safety data for the range of exposures expected in the East Asian patient subpopulation are limited.

At the time of approval, no simeprevir dose will be recommended for patients of East Asian descent due to the paucity of safety data. While some studies have suggested that the incidence of HCV infection is higher in Asian Americans compared to Americans of other ethnic backgrounds, the size of the HCV-infected Asian American subpopulation is relatively small (Kim et al. J Clin Gastroenterology 2013) and simeprevir pharmacokinetics, safety, and efficacy in patients of East Asian descent could be more efficiently evaluated in a trial conducted in East Asia. These data would inform simeprevir dose recommendations for patients with East Asian ancestry.

1. 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.”

Analysis of the Phase 3 clinical trial data suggests that there is a positive relationship between simeprevir exposures and the frequency of adverse events (including rash, photosensitivity, pruritus, dyspnea, and increased bilirubin). The elevated simeprevir exposures observed in people with East Asian ancestry, the limited amount of safety data in HCV-infected patients of East Asian descent, and the increased risk of AEs associated with high simeprevir exposures are review issues and collectively underscore the need for further evaluation of simeprevir in patients with East Asian ancestry.

Trial HPC3005 is an evaluation of the pharmacokinetics, safety, and efficacy of simeprevir 100 and 150 mg QD in HCV-infected patients in China and Korea. The results of this trial will inform a dose selection for HCV-infected patients with East Asian ancestry that provides the most favorable risk-benefit ratio.

2. 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?

3. 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.

The randomized controlled safety, efficacy, and pharmacokinetic trial is currently ongoing in HCV-infected patients China and Korea (i.e. patients with East Asian ancestry) and will evaluate safety, efficacy, and systemic simeprevir exposures following administration of placebo or simeprevir 100 or 150 mg QD in combination with pegylated interferon alfa and ribavirin.

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)  
This trial is currently ongoing; the final CSR is expected in Feb 2015.
- 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

4. 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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VICTORIA L TYSON  
11/20/2013

## 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.

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NDA  
Product Name: 205123  
simeprevir

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PMR Description: Conduct a study to determine the phenotypic susceptibility of TMC435 against:

L356F, V406I, or V629I expressed in genotype 1a replicon cultures, individually and in combination with Q80K

R24W, K213R, T358F, P574A, P574S, T610I, or V629I expressed in genotype 1b replicon cultures

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PMR/PMC Schedule Milestones: Final Report Submission: 7/31/ 2014

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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

The emergence of these substitutions was infrequent and the association between these substitutions and reduced efficacy or virologic failure is unclear.

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 goal of the nonclinical study is to determine if expression of these substitutions is associated with a reduction in simeprevir susceptibility in HCV replicon cultures. If so, then these substitutions may be identified in the label as potentially resistance-associated.

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.

Phenotypic analysis in HCV replicon culture.

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

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**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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VICTORIA L TYSON  
11/20/2013

## 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.

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NDA # 205123  
Product Name: simeprevir

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PMC Description: Submit the final study report and datasets for trial HPC3001, entitled, "A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435 versus Telaprevir, both in Combination with PegIFN $\alpha$ -2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior PegIFN $\alpha$  and Ribavirin Therapy."

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PMR/PMC Schedule Milestones: Trial Completion: 6/30/2014  
Final Report Submission: 12/31/2014

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

This is an ongoing trial evaluating simeprevir versus telaprevir (an approved direct-acting antiviral) in combination with pegylated interferon and ribavirin in null and partial responders previously treated with peginterferon/ribavirin therapy.

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."

This Phase 3 trial is evaluating efficacy and safety of simeprevir in combination with pegylated interferon and ribavirin in prior non-responders (null and partial responders) to pegylated interferon and ribavirin therapy. The trial results are needed to confirm efficacy and safety in previously submitted phase 2b trial in this population.

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.

This is a Phase 3 trial that is currently ongoing.

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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VICTORIA L TYSON  
11/20/2013

## 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 205123  
Product Name: simeprevir

---

PMC Description: Submit the final study report and datasets for trial TMC435HPC2002, entitled, “An Exploratory Phase 2a, Randomized, Open-Label Trial to Investigate the Efficacy and Safety of 12 weeks or 24 weeks of TMC435 in Combination with PSI-7977 with or without Ribavirin in Chronic Hepatitis C Genotype 1 Infected Prior Null Responders to Peginterferon/Ribavirin Therapy or HCV Treatment-Naïve Subjects.”

---

PMR/PMC Schedule Milestones: Study/Trial Completion: 02/28/2014  
Final Report Submission: 10/31/2014  
Other: MM/DD/YYYY

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

This is an ongoing trial evaluating an interferon-free regimen in prior peginterferon/ribavirin null responders and treatment-naïve patients

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 goal of the trial is to evaluate efficacy and safety of interferon-free regimen of simeprevir plus PS-7977 (sofosbuvir) plus or minus ribavirin in patients with chronic hepatitis C.

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.

This is a Phase 2a clinical trial that is currently ongoing.

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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VICTORIA L TYSON  
11/20/2013

## 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# 205123  
Product Name: simeprevir

PMR/PMC Description: Submit the final study report and datasets for trial TMC435-TiDP16-C212, entitled, "A Phase 3 Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of TMC435 Plus PegIFN $\alpha$ -2a (Pegasys®) and Ribavirin (Copegus®) Triple Therapy in Chronic Hepatitis C Genotype-1 Infected Subjects who are Co-Infected with Human Immunodeficiency Virus Type 1 (HIV-1)."

---

PMR/PMC Schedule Milestones: Final Study Report: 05/31/2014  
Other: MM/DD/YYYY

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

There are currently no direct acting antiviral drugs approved for treatment of the HIV/HCV coinfectd population.

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."

This trial (currently ongoing) would provide safety and efficacy information on the combination of simeprevir with peginterferon-alfa and ribavirin in the population of HIV-HCV co-infected patients. Individuals co-infected with HIV/HCV have a greater risk of progression to cirrhosis or decompensated liver disease than HCV-mono-infected patients. This accelerated rate is magnified in HIV/HCV-co-infected patients with low CD4 counts.

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.

Phase 3 open-label clinical trial.

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

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**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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VICTORIA L TYSON  
11/20/2013

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

<b>Product Title<sup>1</sup></b>	<b>TRADENAME™ (simeprevir) capsules, for oral use</b>
Applicant	Janssen Products, LP
Application/Supplement Number	NDA 205123
Type of Application	Original
Indication(s)	treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen
Office/Division	OAP/DAVP
Division Project Manager	Victoria Tyson
Date FDA Received Application	March 28, 2013
Goal Date	November 28, 2013
Date PI Received by SEALD	November 19, 2013
SEALD Review Date	November 19, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> 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

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## 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:**

- NO** 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 > 1/2 page; see page 2 of the Labeling Review Tool (LRT) for suggestions on how to reduce the HL length.

- 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:**

- YES** 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:**

- 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 the Product Title heading.

- 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

## Selected Requirements of Prescribing Information

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

- NO** 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:** "*OLYSIO*" should be inserted in place of "*TRADENAME*".

#### 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. Approval:**" followed by the **4-digit year**.

**Comment:** *The 4-digit year is missing and should read: "2013".*

## Selected Requirements of Prescribing Information

### 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

**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.

## Selected Requirements of Prescribing Information

### 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

- NO** 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: *The statement currently reads: "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient information." and should read: "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."*

#### 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: *The date is missing and should read: "11/2013".*

## Selected Requirements of Prescribing Information

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### 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:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- 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.

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

***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:** Two places in the FPI (Section 1 and subsection 12.4) cross-reference "Pharmacogenomics" where "Clinical Pharmacology" (12.5) should be cross-referenced. Multiple places (2.1, 2.4, 2.5, 5.6, 7, 7.3 [including the heading of Table 5 and its corresponding legend], 8.5, 8.6, 8.7, 8.8, 10) cross-reference "Pharmacokinetics" and should cross-reference "Clinical Pharmacology"(12.3). In subsection 5.2, Patient Counseling Information (17.2) is cross-referenced; this should be removed as prescribers should only be directed to sections with more detailed information and there is no subsection "17.2". Section 6 cross-references "Pregnancy" and should cross-reference "Use in Specific Populations" (8.1). Subsection 12.3 cross-references "Use in Special Populations" under 'Hepatic Impairment' and 'Race' where "Use in Specific Populations" should be cross-referenced.

- 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:

## Selected Requirements of Prescribing Information

“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** 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:**

APPEARS THIS WAY ON ORIGINAL

# 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](http://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/  
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ELIZABETH A DONOHOE  
11/19/2013

ERIC R BRODSKY  
11/19/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

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

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

**Memorandum**

**Date:** October 28, 2013

**To:** Victoria Tyson, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Kemi Asante, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 205123 – TRADENAME (simeprevir) Capsules

---

As requested in DAVP's consult dated April 22, 2013, OPDP has reviewed the simeprevir prescribing information (PI), patient package insert (PPI) and carton/container labeling.

OPDP's comments on the PI are provided directly below in the proposed substantially complete version of the PI sent via email by DAVP on September 18, 2013. 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\NDA205123\205123.enx](#).

Thank you for your consult. If you have any questions please contact me at 301-796-7425 or at [Kemi.Asante@fda.hhs.gov](mailto:Kemi.Asante@fda.hhs.gov).

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/s/  
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OLUWASEUN A ASANTE  
10/28/2013

**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: October 28, 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: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Kemi Asante, 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 (simeprevir)

Dosage Form and Route: Capsules for oral use

Application Type/Number: NDA 205123

Applicant: Janssen Research & Development, LLC

## 1 INTRODUCTION

On March 28, 2013, Janssen Research & Development, LLC submitted for the Agency's review an original New Drug Application (NDA) 205123 for TRADENAME (simeprevir) Capsules. The proposed indication for TRADENAME (simeprevir) Capsules is for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavarin, in adults with compensated liver disease (including cirrhosis).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on April 23, 2013, and April 22, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (simeprevir) Capsules.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (simeprevir) Capsules PPI received on March 28, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 18, 2013.
- Draft TRADENAME (simeprevir) Capsules Prescribing Information (PI) received on March 28, 2013 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 18, 2013.
- Approved Incivek (telaprevir) comparator labeling dated April 25, 2013, and approved Victrelis (boceprevir) comparator labeling dated September 18, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> 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. We have reformatted the PPI document using the Verdana font, size 11.

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 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/  
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SHARON R MILLS  
10/28/2013

OLUWASEUN A ASANTE  
10/28/2013

BARBARA A FULLER  
10/28/2013

LASHAWN M GRIFFITHS  
10/28/2013

**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: October 3, 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

Drug Name and Strength: Sovriad (Simeprevir) 150 mg Capsules

Application Type/Number: NDA 205123

Applicant/sponsor: Janssen

OSE RCM #: 2013-844

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

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1.1	Product Information.....	1
2	Methods and Materials Reviewed.....	1
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3	Medication Error Risk Assessment.....	2
3.1	Labeling Risk Assessment .....	2
4	Conclusions and Recommendations .....	2
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## 1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Sovriad (Simeprevir) 150 mg Tablets, NDA 205123 for areas of vulnerability that could lead to medication errors.

### 1.1 PRODUCT INFORMATION

The following product information is provided in the April 12, 2013 submission.

- Active Ingredient: Simeprevir
- Indication of Use: the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.
- Route of Administration: Oral
- Dosage Form: Capsule
- Strength: 150 mg
- Dose and Frequency: one capsule of 150 mg taken orally once daily with food
- How Supplied: Bottles of 28 capsules and bottles of 7 capsules (emergency supply)
- Storage: Store in the original bottle in order to protect from light. Do not store above 30°C (86°F).
- Container and Closure System: The container closure system for commercial supply is a <sup>(b) (4)</sup> high density polyethylene (HDPE) bottle <sup>(b) (4)</sup>.

## 2 METHODS AND MATERIALS REVIEWED

### 2.1 LABELS AND LABELING

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

- Container Labels submitted April 12, 2013 (Appendix A)
- Insert Labeling submitted April 12, 2013

---

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

### 3 MEDICATION ERROR RISK ASSESSMENT

#### 3.1 LABELING RISK ASSESSMENT

DMEPA reviewed the proposed insert labeling and container labels. We find that the insert labeling does not contain any vulnerabilities that may pose risks for medication errors to occur at this time. However, after review of the container labels, we have identified the following vulnerabilities that may pose a risk for medication errors to occur:

- The proposed proprietary name and established name is in all upper case instead of title case.
- The proposed proprietary name is difficult to read [REDACTED] (b) (4).
- The established name is not prominent enough and difficult to read [REDACTED] (b) (4).
- The strength statement is too prominent and competes with prominence of the proposed proprietary name.
- The alert on the side panel is important information and should be on the principal display panel (PDP).
- The dosage form “capsule” is presented as part of the strength statement. It is customary to present the dosage form next to the established name.
- Emergency supply statement is inappropriate.

### 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the insert labeling is acceptable from a medication error perspective. However, the proposed container labels can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Comments to the Applicant
  - a. Ensure that the proposed proprietary name and established name is title case and not in all uppercase lettering for ease of readability.
  - b. Increase the prominence of the established name so that it is commiserate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
  - c. Move the “Each capsule contains...” statement from the PDP to the side panel and replace with the “Alert...” statement that is currently located on the side panel as this statement provides important information to patients.

- d. Relocate the dosage form “capsule” to the established name statement “simeprevir” as the following demonstrates, since the dosage form is part of the established name:

(Simeprevir) Capsules

150 mg

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

APPEARS THIS WAY ON ORIGINAL

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

#### **Appendix B:** Container Labels



(b) (4)



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/s/  
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JAMIE C WILKINS PARKER on behalf of MORGAN A WALKER  
10/17/2013

JAMIE C WILKINS PARKER  
10/17/2013

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: September 20, 2013

TO: Victoria Tyson, Regulatory Health Project Manager  
Adam Sherwat, M.D. Clinical Reviewer  
Division of Antiviral Drug Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 205-123

APPLICANT: Janssen Research & Development, LLC.

DRUG: TMC435 (Simepravir)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review

INDICATION: Treatment of chronic hepatitis C, genotype 1 infection in treatment naïve and experienced adults with compensated liver disease including cirrhosis.

CONSULTATION REQUEST DATE: April 15, 2013

DIVISION ACTION GOAL DATE: November 22, 2013

INSPECTION SUMMARY GOAL DATE: August 28, 2013; extended to September 28, 2013

PDUFA DATE: November 28, 2013

## **I. BACKGROUND:**

TMC 435, formerly known as TMC345350, is a NS3/4N protease inhibitor (PI) and has been developed for treatment of chronic hepatitis C virus (HCV) infection. The applicant is seeking the following indication: the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin. This product must not be used as monotherapy. Two pivotal studies in HCV-infected relapsed subjects were submitted in support of the application.

**Protocols:** TMC435-HPC3007 entitled “A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon Alfa-2a and Ribavirin in Hepatitis C, Genotype 1 Infected Subjects Who Relapsed After Previous Interferon-Based Therapy” (PROMISE) and

TMC435-TiDP16-C216 entitled “A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) or Peginterferon Alfa-2b (Peginterferon) and Ribavirin (Rebetol) in Treatment Naïve, Genotype 1, Hepatitis C, Infected Subjects” (QUEST-2)

### **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 yielded a sustained virologic response in approximately 45% of treatment naïve subjects infected with genotype 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.

Tibotec Inc has developed TMC435 (simeprevir), because of a need for new compounds that may overcome the disadvantages of current HCV therapy. In recent clinical studies, new investigational drugs acting directly on the virally encoded protease target have 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 NS3/4A protease is essentially for viral replication and multidisciplinary discovery research

has led to new specific and potent NS3/4A protease inhibitors (PIs), including TMC 435. TMC 435 was developed as an oral solution or as a capsule formulation. In HCV-infected subjects, the  $t_{1/2}$  was approximately 41 hours, a profile that supports a once daily dosing regimen, and the lack of a relevant effect of food on the extent of absorption of TMC following an oral capsule.

TMC435 (simeprevir) 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 TMC435-TiDP16-C216, a phase 3 trial comparing TMC 435 vs placebo in treatment–naïve genotype 1 HCV- infected subjects.

### **Protocol TMC-435-HPC3007**

The objective of this study was to demonstrate the superiority of TMC 435 versus placebo a part of a treatment regimen including PegIFN alpha-2a and RBV, with respect to the proportion of subjects with sustained viral response (SVR) 12 weeks after planned end of treatment (SVR12) as defined 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 demonstrate the superiority of TMC 435 versus placebo a part of a treatment regimen including PegIFN alpha-2a and RBV, with respect to the proportion of subjects with SVR 24 weeks after planned end of treatment (SVR24), and 2) to compare the incidence of on-treatment failure in the TMC435 and placebo treatment groups.

This protocol was a randomized, double-blind, placebo–controlled, 2-arm, multicenter, phase III study to compare the efficacy, tolerability and of TMC 435 versus placebo as part of a treatment regimen including PegIFNalpha-2a and RBV in adult HCV, genotype 1 infected subjects who received at least 24 weeks of an Peg IFN-based therapy and relapsed within 1 year after the last medication intake. The study consisted of a screening period with a maximum duration of 6 weeks, a response–guided 24 or 48 week (TMC435 treatment group) or 48-week (control group) treatment period, and a post-therapy follow-up period for up to 72 weeks after the start of treatment. A target of 375 subjects with documented chronic genotype 1 HCV infection, who relapsed and have a screening plasma HCV RNA level of > 10,000 IU/mL were be randomly assigned in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

### **Protocol TMC-435-TiDP16-C216HP**

This protocol was a randomized, double-blind, placebo-controlled, 2-arm, multicenter, phase III study to compare the efficacy, tolerability and of TMC 435 versus placebo as part of a treatment regimen including PegIFNalpha-2a/RBV or PegIFNalpha-2b/ RBV in adult naïve subjects with genotype 1 HCV infection. The study consisted of a screening period with a maximum duration of 6 weeks, a response-guided 24 or 48 week (TMC435 treatment group) or 48-week (control group) treatment period, and a post-therapy follow-up period for up to 72 weeks after the start of treatment.

The objective of this study was to demonstrate the superiority of TMC 435 versus placebo a part of a treatment regimen including PegIFN alpha-2b and RBV, with respect to the proportion of subjects with sustained viral response (SVR) 12 weeks after planned end of treatment (SVR12) 12 weeks after planned end of treatment (SVR12) as defined 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 demonstrate the superiority of TMC 435 versus placebo a part of a treatment regimen including PegIFN alpha-2a and RBV, or PegIFN alpha-2b/RBV, with respect to the proportion of treatment naïve genotype1 HCV-infected subjects with SVR 24 weeks after planned end of treatment (SVR24), and 2) to compare the incidence of on-treatment failure in the TMC435 and placebo treatment groups.

The review division requested inspection of four clinical investigators two domestic and two foreign site inspections in support of this NDA which includes the above protocols. The consult to OSI states, “The sites were selected on the basis of the relatively large enrollment of subjects, high treatment responders, protocol violations, and significant primary efficacy results pertinent to decision-making”.

**II. RESULTS (by protocol/site):**

District	Name of CI/Address/ and Site #	Protocol #s and # of Subjects	Inspection Dates	Final Classification
Dallas	Eric Lawitz, M.D. Alamo Medical Research 621 Camden St. Ste 202 San Antonio TX 78215 Site# US00897	TMC 435- HPC3007 13 subjects	5/17- 24/2013	VAI
Los Angeles	Franco Felizarta, M.D. The Office of Franco Felizarta 3535 San Dimas St. Suite 24 Bakersfield CA 93301 Site # US00643	TMC 435- HPC3007 12 subjects	5/20- 24/2013	VAI
Foreign	Andrzej Horban, M.D. 37 Wolska Street Warszawa 01-201 Poland Site# PL0005	TMC435-TiDP- C216 14 subjects	6/24- 27/2013	Pending (preliminary classification NAI)
Foreign	Ewa Janczewska-Kazak, M.D. UI Koscielna 5 Czeladz 41-250 Poland Site#PL00027	TMC435-TiDP- C216 17 subjects	9/16- 20/2013	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 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. **Eric Lawitz, M.D.**  
**San Antonio TX 78215**

**a. What Was Inspected:** At this site, 13 subjects were screened, and four subjects were reported as screen failures. Nine (9) subjects were randomized into the study, one subject withdrew, and eight subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed. The review included consent forms, drug accountability records, vital signs, IRB files, laboratory results, financial disclosure statement, inclusion/exclusion criteria, and use of

concomitant medications. Source documents for all subjects were compared to case report forms and data listings, to include primary efficacy endpoint and adverse events.

**b. General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Lawitz. However, our investigation found that the clinical investigator did not follow the protocol inclusion/exclusion criteria. Study protocol TMCHPC3007 prohibits the use of CYP inducers according to the protocol. Subject 3007-6448 was on concomitant prohibited medication (Provigil 100mg) for fatigue at the pre-study and throughout the study. The clinical investigator agreed with the observation and stated that in the future when in doubt he will consult with the sponsor for additional information. 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:** With the exception of the item noted above, the records reviewed were found to be organized and the data verifiable. The data in support of the clinical efficacy and safety at Dr. Lawitz's site are considered reliable and acceptable in support of the application.

2. **Franco Felizarta, M. D.  
Bakersfield CA 93301**

**a. What Was Inspected:** At this site, a total of 13 were screened and 4 subjects were reported as screen failures. Forty three subjects were randomized, and four subjects were reported as screen failures. Nine (9) subjects were randomized into the study, and nine subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment except for Subject 3007-6072.

The medical records/source data for all subjects enrolled were reviewed which included consent forms, drug accountability records, vital signs, laboratory results, IRB records, adverse events, prior and current medications, and inclusion/exclusion criteria. There was no evidence of under-reporting of adverse events. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site.

**b. General Observations/Commentary:** At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Felizarta. Our investigation noted that the clinical investigator did not follow the protocol inclusion criteria.

Study protocol TMC435-HPC3007 required that each subject must give written consent before performance of any study related activity. Subject 3007-6072 underwent screening procedures prior to signing a consent form approved by the IRB. The clinical investigator agreed with the observation and stated that the consent form signed by the subject was from a sister study approved by the IRB. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no known limitations to the inspection.

**c. Assessment of Data Integrity:** With the exception of the item noted above, the data generated at Dr. Felizarta’s site in support of the clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

**3. Andrzej Horban, M.D.  
Warszaw, Poland**

**a. What Was Inspected:** At this site, a total 14 subjects were screened, 14 subjects were randomized into the study, and 14 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for five subjects were reviewed for primary/secondary endpoints and informed consent including medical notes being translated from Polish to English. The medical records/source documents for three subjects were reviewed excluding medical notes being translated. Even though the study site was blinded to efficacy endpoints, the field investigator was able to verify documentation of subject visits, sample collection and the contract lab performing the HCV RNA analysis. The review included drug accountability records, vital signs, IRB files, laboratory tests, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were not verified/compared to case report forms and data listings for the primary efficacy endpoints. However, our field investigator was able to verify adverse events reporting.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr.Horban. The medical records reviewed were found to be in order, organized, and certain data were 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 submitted in support of the clinical efficacy and safety at Dr. Horba’s site are considered reliable and appear acceptable in support of the pending application.

**4. Ewa Janeczewska-Kazak, M.D.  
Czelade 41-250, Poland**

**a. What Was Inspected:** At this site, a total 17 subjects were screened, two subjects were reported as screen failures, 15 subjects were randomized into the study, and 11 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 15 subjects were reviewed for primary/secondary endpoints and informed consent including medical notes being translated from Polish to English. The medical records/source documents for 15 subjects were reviewed. The review included drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications.

Source documents for all subjects were compared to case report forms and data listings for the primary efficacy endpoints. However, there was a third party unblinded monitor to review the primary efficacy endpoint and write a note to the site for determination of successful/acceptable primary efficacy endpoint results. This procedure was completed according to the protocol.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Janczewska-Kazak. The medical records reviewed were found to be in order, organized, and certain data were 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 submitted in support of the clinical efficacy and safety at Dr. Janczewska-Kazak's site are considered reliable and appear acceptable in support of the pending application.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspections of Drs. Lawitz and Felizarta revealed minor regulatory violations, and the classifications for these inspections are noted above as Voluntary Action Indicated (VAI). The classification for the inspection of Drs. Horban and Janczewska-Kazak are pending with No Action Indicated (NAI). The final classification for Dr. Horban's and Janczewska's sites will be determined upon review of the establishment inspection reports (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. While minor observations were identified during the inspection of Drs. Lawitz and Felizarta, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect of the violations on overall data integrity to be significant. Overall, the data submitted from these three 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 Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

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

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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.**  
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/s/  
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ANTOINE N EL HAGE  
09/26/2013

KASSA AYALEW  
09/26/2013

**M E M O R A N D U M**

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

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DATE: September 16, 2013

TO: Debra B. Birnkrant, M.D.  
Director, Division of Antiviral Products  
Office of Antimicrobial Products

FROM: Xikui Chen, Ph.D.  
Pharmacologist  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations (OSI)  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 205-123, Simeprevir  
Capsules, sponsored by Janssen Research and  
Development, LLC

At the request of the Division of Antiviral Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the following study:

**Study Number:** TMC435HPC1002  
**Study Title:** "A Phase I, open-label, randomized, 3-panel, 3-way crossover trial in healthy adult subjects to assess the relative bioavailability of TMC435 following administration of 2 liquid formulations or 2 different capsule concept formulations compared to the Phase III 150 mg capsule, and to assess the effect of food on the bioavailability of TMC435 following administration of the liquid formulations"

The audits included thorough examination of study records, facilities, and equipment, and interviews and discussions with the firms' managements and staff.

**Clinical Site:**

The inspection of the clinical portion was conducted by ORA Investigator (b) (4). Following the inspection (b) (4) Form FDA-483 was i (b) (4) (Attachment the response from (b) (4) to the inspectional findings on Se (b) (4), 2013 (Att 2). The Form FDA-483 observations, (b) (4) response, and the DBGLPC reviewer's evaluations f (b) (4)

- 1. You failed to retain reserve samples for the test article and reference standards used to conduct the bioequivalence study TMC435HPC1002. The remaining test articles and reference standards used for this trial were returned to the Sponsor at the end of trial. The return of study supplies were picked up by the courier on 16July2012, according to the (b) (4) Record of Return of Study Supplies to Sponsor form.**

(b) (4) responded that this study does not meet the requirements FR 320.38(b) (1), (b) (2), or (b) (3). The study compared the relative bioavailability of two pediatric formulations (a solution and a suspension) defined as test articles, with the II testing capsule of TMC435 as reference standard.

(b) (4) forwards the claim by the sponsor Janssen that they are king approval of the solution or suspension formulations and will not do so in the future [Reference 2]. DBGLPC is not aware when Janssen made these decisions relative to the timing of the proposed

design (b) (4) processes. Batch 1 (b) (4)

(b) (4) G019 (b) (4)

Both batches of G019 have the same formulation as the phase III capsule of TMC435 tested in study TMC435HPC1002.

DBGLPC defers to DAVP and OCP to decide whether all or part of study TMC435HPC1002 should be considered as a definitive bioavailability/bioequivalence study, for which reserve samples would be required.

2. You did not retain documentation showing you reported deviations in PK (pharmacokinetic) sample collection times when they were collected from subjects outside the signed Window Allowance Agreement. Study protocol No. TMC435HPC1002, approved date 21FEB2012, Section 17.1 indicates [that] when departures from the protocol occur, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action.

(b) (4) provided an email [Reference 6], which concluded that all PK sampling time deviations, including those outside the Window Allowance Agreement, were minor and not major protocol deviations, and that there was no impact on trial data or subject safety.

DBGLPC defers to DAVP and OCP to evaluate the impact of the sampling time deviations.

**Bioanalytical Site:**

The inspectio  
Investigator

(b) (4) Following the inspection (b) (4), Form FDA-4 (b) (4) issued (**Attachment 3**) (b) (4) d a response from (b) (4) to the inspectional finding on S (b) (4), 2013 (**Atta** (b) (4)). The Form FDA-483 observation, (b) (4) response, and the DBGLPC reviewer's evaluation

1. For Study TMC435HPC1002, analytical run #18 did not include dilution quality control (QC) samples in measurements of TMC435 for 5/5 clinical plasma samples, with concentrations that were above the upper limit of quantification (ULOQ).

In the response, (b) (4) reported a 2-fold dilution linearity experiment using (b) (4) control samples with concentrations above ULOQ. The results for accuracy and precision are within the acceptance criteria for the experiment and listed in Amendment 2 of partial validation report number SH-J01-R618A2/BA1238.

Quality control samples were used for evaluating dilution linearity, because the study plasma samples were not available. The data for 5 study samples with concentrations above ULOQ,

assayed with 2-fold dilution, are acceptable based on the results of the dilution linearity experiment.

**Conclusion:**

Following the above inspections, this DBGLPC reviewer recommends the following:

- DAVP and OCP should determine whether Study TMC435HPC1002 should be considered as a definitive bioavailability/bioequivalence study, for which reserve samples would be required. Without the reserve samples, the study would not be acceptable for review as a definitive study. The study is acceptable for other limited purposes, such as comparing manufacturing lots.
- The bioanalytical data from study TMC435HPC1002 are acceptable for review, if the clinical data are accepted by DAVP and OCP.

APPEARS THIS WAY ON ORIGINAL

**Final Classifications:**

VAI:

(b) (4)

VAI:

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Bonapace/Choi/Skelly/Dejernett/Chen/CF

OND/ODE4/DAVP/Victoria Tyson/Birnkrant

(b) (4)

Draft: XC 9/13/2013

Edit: MFS 9/13/2013; WHT 9/13/2013

OSI: BE File # 6455; O:\BE\EIRCOVER\205123.jan.sim.doc

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good

Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1514697

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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.**  
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/s/  
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XIKUI CHEN  
09/16/2013

MICHAEL F SKELLY  
09/16/2013  
Skelly signing on behalf of Dr. Haidar

WILLIAM H TAYLOR  
09/17/2013

## 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 # 205123 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD (Sovriad conditionally granted under IND; submitted to NDA and under review) Established/Proper Name: Simeprevir, TMC435 Dosage Form: Capsule Strengths: 150 mg		
Applicant: Janssen Research & Development, LLC Agent for Applicant (if applicable):		
Date of Application: March 28, 2013 Date of Receipt: March 28, 2013 Date clock started after UN:		
PDUFA Goal Date: November 28, 2013		Action Goal Date (if different): November 22, 2013
Filing Date: May 27, 2013		Date of Filing Meeting: April 22, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication: treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin		
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)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<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 type="checkbox"/> Separate products requiring cross-labeling <input checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<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): 75391				
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>	✓			
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>	✓			Sovriad-trade name granted 9/20/12 under IND 75391; submitted to the NDA 4/12/2013
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: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		✓		
<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>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<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><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></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>✓</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>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>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>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></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																
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><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>✓</p>																		

<p><b>Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>				
<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	✓			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		✓		
<p><b>If yes</b>, 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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

<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)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<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?	✓			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<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>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	✓			
<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>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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, <b>both</b> 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&amp;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>	✓			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> 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>			✓	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>			✓	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			PeRC Meeting-9/25/2013
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		✓		
<p><b>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?</b></p> <p><i>If no, request in 74-day letter</i></p>	✓			PPSR; Partial waiver-Less than 3 years of age Deferral-3 years of age to less than 18 years of age
<p><b>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)?</b></p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p><b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b></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)<sup>3</sup></i></p>			✓	
<p><b><u>Proprietary Name</u></b></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>	✓			submitted to NDA 4/12/13
<p><b><u>REMS</u></b></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>		✓		
<p><b><u>Prescription Labeling</u></b></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) <input type="checkbox"/> Instructions for Use (IFU)			

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

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

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

4

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	✓			DDDP- skin rash; Validation of manufacturing controls and analytical methods
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> October 18, 2010, September 15, 2011	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> August 2, 2012, January 30, 2013	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			✓	

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** April 22, 2013

**BLA/NDA/Supp #:** 205123

**PROPRIETARY NAME:** TBD (proposed name Sovriad under review)

**ESTABLISHED/PROPER NAME:** Simeprevir, TMC435

**DOSAGE FORM/STRENGTH:** 150 mg, Capsules

**APPLICANT:** Janssen Research & Development, LLC

**PROPOSED INDICATION:** in combination with pegylated interferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in adults with compensated liver disease including cirrhosis who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin

**BACKGROUND:**

TMC435, simeprevir, is an NS3/4A protease inhibitor, a 150 mg capsule proposed for administration once daily in combination with pegylated interferon alfa and ribavirin for 12 weeks, followed by response-guided therapy for 12 or 36 weeks of P/R, based on the response at Week 4. Clinical trials to support the indication were conducted at several sites in the U.S. and in foreign countries under IND 75391.

The NDA includes additional pharmacogenomics and deep sequencing data from trials C205 and C206 that were conducted in treatment-naïve and treatment-experienced, genotype 1 CHC subjects. The NDA also includes Phase 1, 2, PK, BA, BE and drug-drug interaction trials and Janssen has ongoing studies in CHC/HIV co-infected subjects (C212) and in treatment-naïve and treatment-experienced patients infected with Genotype 4.

The NDA includes a request for priority review designation.

The trade name Sovriad was granted under the IND on September 20, 2012 and a request for review was submitted to the NDA for review on April 12, 2013. The goal date for response is July 11, 2013.

A pediatric development plan is included in the NDA along with a request for waiver of pediatric studies for children under 3 years of age and a deferral for children 3 to less than 18 years of age.

Administratively the NDA is complete and is being managed under PDUFA V-The Program. There were no agreements made at the application's pre-submission meeting regarding late submission components. The following changes were highlighted under PDUFA V:

- Filing Letter-Date of the Internal MidCycle Meeting

- Post MidCycle Teleconference
- Late-Cycle Meeting

An Advisory Committee Meeting is scheduled for October 24, 2013.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Victoria Tyson	Y
	CPMS/TL:	Elizabeth Thompson, MS	Y
Cross-Discipline Team Leader (CDTL)	Mary Singer, MD, Ph.D.		Y
Clinical	Reviewer:	Adam Sherwat, MD	Y
	TL:	Mary Singer, MD, Ph.D.	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Damon Deming, Ph.D. Eric Donaldson, Ph.D.	Y Y
	TL:	Julian O'Rear, Ph.D.	Y

Clinical Pharmacology	Reviewer:	Leslie Chinn, Ph.D.	Y
	TL:	Islam Younis, Ph. D.	N
Biostatistics	Reviewer:	Yanming Yin, Ph.D.	Y
	TL:	Fraser Smith, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Janice Lansita, Ph.D.	Y
	TL:	Hanan Ghantous, Ph.D., DABT	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Celia Cruz, Ph.D.-Drug Product Chunchun Zhang, Ph.D.- Drug Substance	Y Y
	TL:	Stephen Miller, Ph.D. Rapti Madurawe, Ph.D.	Y N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Danyal Chaudhry	Y
	TL:	Franklin Stephenson	N
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:	Kendra Worthy	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	Y
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<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"> <li>• Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments  <b>List comments:</b></li> </ul>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?  <b>If no, explain:</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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 disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: October 24, 2013 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></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"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b> deep sequencing data trials C205 and C206</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><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> pharmacogenomics data submitted for trials C205 and C206</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"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul> <p>BA and analytical Site</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></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

<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<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
<b>Comments:</b>	

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<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></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><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments: EES submitted</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></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><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<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"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Ed Cox/Jeff Murray</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): June 20, 2013</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p>	

<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<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 type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" 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>
<b>ACTIONS ITEMS</b>	
<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"> <li>• 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)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<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><a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a>]</p>
<input type="checkbox"/>	Other

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## 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.

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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.**  
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/s/  
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VICTORIA L TYSON  
05/07/2013

ELIZABETH G THOMPSON  
05/07/2013

# **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:** 205123

**Application Type:** New NDA

**Name of Drug:** TBD (simeprevir) Capsule

**Applicant:** Janssen Research & Development, LLC

**Submission Date:** March 28, 2013

**Receipt Date:** March 28, 2013

## **1.0 Regulatory History and Applicant's Main Proposals**

NDA 205123 was submitted March 28, 2013 and is both a Type 1 NME and Type 4 New Combination. This proposed indication is for the treatment of genotype 1 hepatitis C infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve or who failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

## **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.

## 4.0 Appendix

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### 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.

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### 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

## Selected Requirements of Prescribing Information (SRPI)

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

**YES**

## Selected Requirements of Prescribing Information (SRPI)

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:

### 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**”).

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

YES

## Selected Requirements of Prescribing Information (SRPI)

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:

### 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

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

Comment: Applicant only listed contraindications for the coadministered products and did not indicate any contraindications for simeprevir. Applicant will be asked to state "None" if no contraindications to simeprevir are known.

- NO** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: See comment above. Applicant should list bullet each contraindication.

### 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:

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## Contents: Table of Contents (TOC)

## Selected Requirements of Prescribing Information (SRPI)

### 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.  
*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:*
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## 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.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>

## Selected Requirements of Prescribing Information (SRPI)

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

**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**”).

## Selected Requirements of Prescribing Information (SRPI)

### 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**

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

**Comment:** *Applicant only listed contraindications for the coadministered products and did not indicate any contraindications for simprevir. Applicant will be asked to state "None" if no contraindications to simeprevir are known.*

#### **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:

*“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:** *Comment will be sent to sponsor to remove italicized font.*

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/s/  
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