APPLICATION NUMBER:

209394Orig1s000

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.

NDA/BLA #: 209394
Product Name: MAVYRET; glecaprevir and pibrentasvir film coated tablets

PMR/PMC Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C virus infection

PMR/PMC Schedule Milestones: Final Protocol Submission: January 2017
Study/Trial Completion: July 2022
Final Report Submission: January 2023
Other: 

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

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

Adult studies are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on June 26, 2017. The PeRC agreed with the Division to grant a deferral for pediatric patients aged 3 through 17 years because the product is ready for approval in adults.

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.”
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
  - [x] 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.**

A clinical trial is required to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C infection.
Required

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

Continuation of Question 4

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

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

Agreed upon:

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

☐ 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.

_______________________________________

(signature line for BLAs)
PMR/PMC Development Template

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

### NDA/BLA #
NDA 209394

### Product Name:
Mavyret™ (Glecaprevir and Pibrentasvir)

### PMR/PMC Description:
Submit the final SVR12 report and datasets, including drug resistance datasets, for the ongoing clinical trial M16-126, evaluating glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection.

### PMR/PMC Schedule Milestones:

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>11/17/2016</td>
</tr>
<tr>
<td>Study/Trial Completion</td>
<td>08/01/2018</td>
</tr>
<tr>
<td>Final SVR12 Report Submission</td>
<td>03/31/2019</td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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.

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

Chronic HCV infection is a serious and life-threatening disease. NDA 209394 for glecaprevir/pibrentasvir will likely be approved for the treatment of patients with chronic HCV infection, including all 6 major HCV genotypes (1-6). This regimen will address current unmet medical needs for selected populations including HCV genotype 1 infected patients who previously failed treatment with an NS5A inhibitor-containing regimen, as well as HCV genotype 2, 3, 5 or 6 infected patients with severe renal impairment. For patients without cirrhosis, the regimen is highly effective with a short, 8-week treatment duration, which will be recommended for those who are treatment-naïve (any HCV genotype), or interferon, ribavirin or sofosbuvir treatment-experienced (any HCV genotype except genotype 3). This duration is shorter than current recommended durations for HCV treatment. Clinical trial data directly supporting the 8-week duration are primarily from patients with HCV genotypes 1-4, with relatively limited data from patients with HCV genotype 5 (n=2) or genotype 6 (n=10). Additional supportive clinical trial and in vitro (i.e., cell culture experiments) data were used to justify the same 8-week duration for HCV genotypes 5 and 6 that is being recommended for other HCV genotypes. Patients with HCV genotypes 5 and 6 are challenging to enroll in clinical trials as these are the least prevalent genotypes both in the U.S. and worldwide, accounting for ≤1% of U.S. HCV infections.

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.”
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.

| An open-label clinical trial (M16-126) that will address this PMC is ongoing. The trial is evaluating glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection. |   |   |

Reference ID: 4130395
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.

_______________________________________

(signature line for BLAs)
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 209394
Product Name: MAVYRET; glecaprevir and pibrentasvir film coated tablets

PMR/PMC Description: Submit the final SVR12 clinical study report and datasets for the ongoing trial M14-730 (EXPEDITION-2) to provide additional efficacy and safety data in HIV/HCV co-infected subjects receiving glecaprevir and pibrentasvir.

PMR/PMC Schedule Milestones: Final Protocol Submission: 07/22/2016
Study/Trial Completion: 04/03/2017
Final SVR12 Report Submission: 10/31/2017
Other: N/A

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
   - [x] Other

M14-730 (EXPEDITION-2) is a trial evaluating the safety and efficacy of glecaprevir and pibrentasvir (GLE/PIB) for 8 or 12 weeks in subjects with chronic HCV infection and HIV-1 co-infection. The study is ongoing during review of the NDA.

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.”

Reference ID: 4130395
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 trial is an ongoing (b)(4) trial evaluating 8 or 12 weeks of GLE/PIB in HCV/HIV-1 coinfected subjects as described above.
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.

_______________________________________

(signature line for BLAs)
PMR/PMC Development Template

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

NDA/BLA # 209394
MAVYRET; glecaprevir and pibrentasvir film coated tablets

Product Name:

PMR/PMC Description: Conduct a study evaluating the efficacy of glecaprevir/pibrentasvir in HCV genotype 1 infected subjects with prior treatment experience with an NS5A inhibitor plus sofosbuvir regimen.

PMR/PMC Schedule Milestones:

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>5/30/2017</td>
</tr>
<tr>
<td>Study/Trial Completion</td>
<td>12/31/2018</td>
</tr>
<tr>
<td>Final SVR12 Report Submission</td>
<td>6/30/2019</td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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

Glecaprevir/pibrentasvir will likely be approved for the treatment of HCV genotype 1 infected patients with prior NS5A inhibitor treatment experience, who are naïve to NS3/4A protease inhibitors. The recommended treatment regimen will be glecaprevir/pibrentasvir for 16 weeks, based on an observed SVR12 rate of 94% (16/17). Ten of these 17 subjects previously received an NS5A inhibitor (ledipasvir) plus sofosbuvir regimen, while the other 7 subjects previously received a daclatasvir plus pegylated interferon-alpha/ribavirin regimen. While the results are encouraging and support approval for this population, more efficacy and resistance data are desired in the NS5A inhibitor plus sofosbuvir experienced 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.”
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.

The purpose of this PMC is to obtain additional efficacy and drug resistance data with the glecaprevir/pibrentasvir regimen in HCV genotype 1 infected patients who previously failed treatment with an NS5A inhibitor plus sofosbuvir regimen, and are NS3/4A protease inhibitor-naïve.
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 or clinical trial performed for effectiveness

- 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.

______________________________
(signature line for BLAs)
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.

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>NDA209394</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Mavyret®</td>
</tr>
</tbody>
</table>

PMR/PMC Description: Conduct a study to characterize the phenotypic effect of the following individual NS3/4A or NS5A substitutions on the cell culture anti-HCV activity of glecaprevir or pibrentasvir, respectively: genotype 1a NS3_I18V, NS3_N77S, NS3_V116A, NS3_I354V and NS4A_V23A, genotype 3a NS3_I366V, and genotype 1a NS5A_A61T.

PMR/PMC Schedule Milestones:
- Final Protocol Submission: N/A
- Study/Trial Completion: N/A
- Final Report Submission: 03/31/2018
- Other: N/A

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
- [x] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

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.”
3. If the study/clinical trial is a PMR, check the applicable regulation. 
   *If not a PMR, skip to 4.*
   
   - **Which regulation?**
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [ ] FDAAA required safety study/clinical trial
   
   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [ ] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?
   
   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [ ] Analysis of spontaneous postmarketing adverse events?
       
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
     
     - [ ] Analysis using pharmacovigilance system?
       
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     
     - [ ] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       
       *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
     
     - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

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

Continuation of Question 4

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

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

- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
  ✗ Nonclinical study, not safety-related (specify)
    The impact of these substitutions on the cell culture anti-HCV activity of glecaprevir or pibrentasvir will be evaluated using the HCV replicon system.

- 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.

______________________________
(signature line for BLAs)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICIA MORUF
07/26/2017

POONAM MISHRA
07/26/2017
Date: June 27, 2017

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)

From: Morgan Walker, PharmD, MBA, CPH
    Patient Labeling Reviewer
    Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
    Regulatory Review Officer
    Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): MAVYRET (glecaprevir and pibrentasvir)

Dosage Form and Route: tablets, for oral use

Application Type/Number: 209394

Applicant: AbbVie Inc.
1 INTRODUCTION

On December 14, 2016, AbbVie Inc. submitted for the Agency’s review a New Drug Application (NDA) 209394 for MAVYRET (glecaprevir and pibrentasvir) tablets. The proposed indication for MAVYRET (glecaprevir and pibrentasvir) tablets is for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection. This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on January 12, 2017, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for MAVYRET (glecaprevir and pibrentasvir) tablets.

2 MATERIAL REVIEWED

- Draft MAVYRET (glecaprevir and pibrentasvir) tablets PPI received on December 14, 2016, and received by DMPP and OPDP on June 15, 2017.
- Draft MAVYRET (glecaprevir and pibrentasvir) Prescribing Information (PI) received on December 14, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 15, 2017.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

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

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

/s/

MORGAN A WALKER
06/27/2017

WENDY R LUBARSKY
06/27/2017

BARBARA A FULLER
06/27/2017
Memorandum

Date: June 27, 2017

To: Alicia Moruf
   Regulatory Project Manager
   Division of Antiviral Products

From: Wendy Lubarsky, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion

Subject: NDA 209394 – MAVYRET (glecaprevir and pibrentasvir) tablets, for oral use

As requested in the Division of Antiviral Products’ (DAVP) consult dated January 12, 2017, the Office of Prescription Drug Promotion (OPDP) has reviewed the MAVYRET (glecaprevir and pibrentasvir) tablets, for oral use prescribing information, patient labeling, and carton/container labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information sent via email by Alicia Moruf on June 15, 2017. OPDP reviewed the substantially complete version of the carton/container labeling sent via email on June 26, 2017, by Alicia Moruf.

OPDP has reviewed the substantially complete prescribing information and carton/container labeling in the attached documents below. We have no comments at this time on the prescribing information. Our one comment below on the carton/container labeling is similar to Valerie Wilson’s comment sent to the sponsor on June 26, 2017.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling under a separate cover on June 27, 2017.
Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------
WENDY R LUBARSKY
06/27/2017
MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 23, 2017
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 209394
Product Name and Strength: Mavyret (glecaprevir and pibrentasvir) Tablet, 100 mg/40 mg
Applicant/Sponsor Name: AbbVie
Submission Date: June 9, 2017
OSE RCM #: 2017-14-1
DMEPA Primary Reviewer: Valerie S. Wilson, PharmD
DMEPA Team Leader (Acting): Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Antiviral Products (DAVP) requested that we review the revised container label and carton labeling for Mavyret (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container labels and carton labeling for Mavyret are unacceptable from a medication error perspective. On May 26, 2017, DAVP requested rationale from AbbVie for inclusion of the statement “(b)(4)” in the prescribing information (PI) and made the recommendation to remove the statement if there is no rationale for inclusion. On June 2, 2017, in response of the May 26, 2017 information request, AbbVie did not provide a rationale and instead choose to remove the statement from the PI. The container label and carton labeling includes the

statement “(b)(4),” which is inconsistent with the Mavyret PI and may result in confusion for tablet administration.

3 RECOMMENDATIONS FOR ABBVIE

We recommend the following be implemented prior to approval of this NDA:

A. Remove the statement “(b)(4)” from each container label and carton labeling to mitigate possible confusion surrounding the administration of the tablets and to be consistent with the DOSAGE AND ADMINISTRATION section of the Mavyret prescribing information.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------------------
VALERIE S WILSON
06/23/2017

JAMES H SCHLICK on behalf of OTTO L TOWNSEND
06/23/2017
1 REASON FOR REVIEW

On December 14, 2016, Abbvie submitted New Drug Application (NDA) 209394 for new molecular entity (NME) glecaprevir and pibrentasvir for the treatment of chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection. The NDA submission included proposed container labels, carton labeling, prescribing information (PI), and human factors (HF) label comprehension validation study results. Thus, DAVP requests we assess the materials from a medication error perspective.
1.1 REGULATORY HISTORY

December 14, 2016: Abbvie developed a 4-week carton packaging for glecaprevir and pibrentasvir fashioned after the Technivie and Viekira XR carton packaging. Additionally, under IND 127416, AbbVie completed a human factors (HF) use-risk assessment and stated in the February 29, 2016 meeting package, that simulated-use and pharmacy simulated testing would not be conducted because 1) it would not further inform the product’s residual risk profile and 2) the residual risk is acceptable. On April 8, 2016, the Agency provided written responses to AbbVie agreeing that simulated-use testing or label comprehension studies were not needed for the proposed container label and carton labeling (Appendix F).

Later, Abbvie developed an 8-week glecaprevir and pibrentasvir carton (“NextGen 8-Week”) to appear on the market with the monthly glecaprevir and pibrentasvir carton (“NextGen 4-Week”) and made the decision to pursue a HF label comprehension validation study. The protocol for the HF study was not submitted for review prior to conducting the study. However, as previously stated, the HF label comprehension validation study results were included in AbbVie’s December 14, 2016 NDA submission.

April 13, 2017: AbbVie submitted an amendment to NDA 209394, pursuant to 21 CFR 314.60, to update the graphical representation of the daily wallet pack (see appendix G). This update is in response to Agency feedback provided to AbbVie on April 6, 2017 (see Appendix F).

April 17, 2017: AbbVie submitted an amendment to NDA 209394, pursuant to 21 CFR 314.60, to update labeling for Sections 2, 6, and 14 of the full prescribing information (FPI) (see Appendix G). This update is in response to Agency feedback provided to AbbVie on April 7, 2017 (see Appendix F).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B (N/A)</td>
</tr>
<tr>
<td>Human Factors Study (Label Comprehension Study Protocol and Validation Results)</td>
<td>C</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D (N/A)</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E (N/A)</td>
</tr>
<tr>
<td>Other (Written Responses, Information Requests, and Email Correspondence)</td>
<td>F</td>
</tr>
</tbody>
</table>
### Table 1. Materials Considered for this Label, Labeling, and Human Factors Review

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A = not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

### 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the labels, labeling, and human factors (HF) label comprehension validation results submitted to NDA 209394 and identified areas for risks to medication errors, that can be addressed through label and labeling revisions. These revisions will not require validation through another HF validation study.

Our assessment of the label comprehension study results, described in sections 3.1.1 (Pharmacy Label Differentiation) and 3.1.2 (Content Knowledge Statement Task), focuses on participant failures in the two parts of the study. We provide our assessment of the “NextGen 4-Week” and “NextGen 8-week” container label and carton labeling in section 3.2.

### 3.1 HUMAN FACTORS VALIDATION STUDY

A detailed summary of the HF label comprehension validation study design and results is located in Appendix C. The HF label comprehension validation study was conducted in two parts 1) a pharmacy label differentiation study and 2) a content statement knowledge task study.

#### 3.1.1 Pharmacy Label Differentiation

The pharmacy label differentiation task consisted of two separate sessions 1) a prescription fill task session performed by 15 pharmacy technicians and 2) a prescription verification task session performed by 15 pharmacists.

**Prescription Fill Task Failures**

Pharmacy technicians were tasked with filling three prescriptions orders of either “NextGen 4-Week,” “NextGen 8-Week,” Technivie, or Viekira XR by selecting the appropriate medication carton from a simulated pharmacy shelf. Two pharmacy technicians failed to fill “NextGen 4-Week” and “NextGen 8-Week” according to the prescription order provided to them, as described in Table 2.
### Table 2. Prescription Fill Task Failures (n=2)

<table>
<thead>
<tr>
<th>Task</th>
<th># of failures</th>
<th>Description of Use Error (Observed and Participant Explanation)</th>
<th>Root Cause Analysis Provided by AbbVie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill 1-month supply of NextGen (glecaprevir/pibrentasvir)</td>
<td>n=1</td>
<td>Observed: Participant filled one monthly “NextGen 4-Week” (glecaprevir/pibrentasvir) carton and added 1 weekly carton from the “NextGen 8-Week” carton to give a “30-day supply.”</td>
<td>Slip/Lapse: Participant did not check the NDC when completing the simulated task.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participant explanation of failure: “…relied solely on the medication name and strength when selecting the carton from the shelf and did not crosscheck the NDC on the carton and medication label...unfamiliarity with medication tablets that are packaged in cartons.”</td>
<td>Negative Transfer: Participant applied training from workplace where the pharmacy staff dispenses medication only in multiples of 30 without consideration of the pre-quantified, weekly amounts that are available in cartons.</td>
</tr>
<tr>
<td>Fill 2-month supply of NextGen (glecaprevir/pibrentasvir)</td>
<td>n=1</td>
<td>Observed: Participant filled one monthly “NextGen 4-Week” carton instead of one “NextGen 8-Week” carton.</td>
<td>Negative transfer: Participant was unable to find the required medication quantity on the label to confirm whether she selected the correct carton. Negative transfer of training regarding identification of critical information from a pharmacy-generated label led to failure when using the simulated pharmacy label provided in the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participant explanation of failure: “…was looking for [the] medication quantity on the prescription order and the medication label but was unable to find it...only checked the medication name when selecting the carton and overlooked the NDC.”</td>
<td></td>
</tr>
</tbody>
</table>

AbbVie did not provide mitigations to address either of the failures observed during the prescription fill task and determined that “policies and procedures used in specialty pharmacy such as pharmacist verification, barcode scanning, and ePrescribing would significantly reduce the likelihood of these failures going unnoticed.”

We determined that a risk for selection error between the “NextGen 4-Week” and “NextGen 8-Week” carton has not been fully addressed. Of particular concern are patients receiving a quantity less than prescribed to complete a full treatment duration and subsequent risk of failure to sustain viral response. Therefore, the “NextGen 4-Week” and “NextGen 8-week” carton labeling should be revised to provide additional distinguishing features and we provide recommendation number 1 through 4 to Abbvie in letter-ready format in section 4.2 to:

1. add the statement “4-Week Supply (84 tablets)” to the upper left corner of the principal display panel (PDP) of the “NextGen 4-Week” carton labeling.
2. revise the statement “8-week” located in the upper left corner of the “NextGen 8-Week” PDP to state “8-week supply (168 tablets)”.

Reference ID: 4097911
3. Enlarge the last two digits (package size) of the NDCs on the “NextGen 4-Week” and “NextGen 8-Week” PDP to read in the format xxxx-xxxx-XX.

4. Consider utilizing the top closure flap of the “NextGen 4-Week” and “NextGen 8-Week” carton to duplicate the information stated on the PDP.

Prescription Verification Task Failures

In a separate session, pharmacist participants were tasked with verifying four different pre-filled orders, including one incorrectly filled order. The incorrectly filled order was of either “NextGen 4-Week,” “NextGen 8-Week,” Technivie, or Viekira XR and pharmacists were expected to identify the incorrectly filled order and then correct it by selecting the correct medication carton from the simulated pharmacy shelf. Four pharmacists failed to correctly perform the prescription verification tasks and one pharmacist was a close call, as described in Table 3.

Table 3. Prescription Verification Task Failures (n=4, failures; n=1, close call)

<table>
<thead>
<tr>
<th>Task</th>
<th># of failures</th>
<th>Description of Use Error (Observed and Participant Explanation)</th>
<th>Root Cause Analysis Provided by AbbVie</th>
</tr>
</thead>
</table>
| Pharmacist needs to identify the incorrectly filled “NextGen” prescription order and correct it. | 1 | **Observed**  
Participant filled two NextGen 4-week cartons instead of one NextGen 8-week carton.  
**Participant Explanation of Failure**  
“I was supposed to fill the other carton. I knew there were supposed to be 2 cartons for 8 weeks. And the big box has 8 weeks.” The participant explained that she did not check NDC during the task because at her workplace, pharmacy technicians and pharmacists use a scanner to cross check the medication label and the product. “We never check manually. We always scan the product before finalizing it.” The participant explained that if the scanner notifies them about an incorrectly selected product, the pharmacist returns the order to the pharmacy technician for correction. | **Negative Transfer**  
The participant relies on additional checks that occur at her workplace via barcode scanners that were not a part of this simulated task. This resulted in a failure to use the NDC code to verify that she had the correct package presentation. |
| Pharmacist needs to identify the incorrectly filled “NextGen” prescription order and correct it. | 1 | **Observed**  
Participant verified a filled prescription containing one “NextGen 4-Week” carton instead of a “NextGen 8-Week” carton as stated on the prescription order.  
**Participant Explanation of Failure**  
The participant stated that there was a mismatch between the NDCs on the medication label and on the carton, which caused him to be concerned. However, he stated that he had opened the carton and verified that the weekly | **Slip/Lapse**  
The participant noticed the incorrect NDC on the 4-week carton but rather than go find the correct carton, he checked the content of the 4-week carton against the label and attempted to manually calculate the quantity included. When doing this, he made a computational error and thought that the quantity of |
cartons contained the correct medication name, strength, and quantity. He said that these all matched, even though the quantity was in fact different, and then still proceeded to approve the incorrectly filled order. The participant additionally explained that he made a mistake when checking the quantity of the medication. “It was a computational error. I thought it was correct for a quantity of 168 tablets. Purely a human error.”

Later in the study session, he added that at his workplace, the staff typically uses a scanner when filling and verifying prescriptions. The participant explained that if the scanner notifies them about a wrong product, the staff would then check the medication name, strength, and quantity inside the package. If all three items match the label, the staff is allowed to overwrite the prescription order and approve the product, despite a mismatched NDC.

| Pharmacist needs to identify the incorrectly filled “NextGen” prescription order and correct it. | 1 | Observed
Participant forgot that simulated pharmacy shelf was available and did not attempt to retrieve the correct prescription. He reversed the insurance claim to fill 4 weeks instead of 8 weeks.

Participant Explanation of Failure
He immediately stated that the NDC on the carton did not match the label. He understood that the order was filled incorrectly, and that the quantity needed to be filled was 168 tablets, and that the filled carton (NextGen 4-week) contained only 84 tablets. He then explained that he would correct the NDC on the label to match the NDC of a 4-week carton, and fill two cartons of a Next Gen 4-week supply. The participant explained that the label he was given was incorrect since the NDC on the label did not match the NDC on the 4-week carton. He stated that he would reverse the insurance claim for the 8-week package and reprocess for the 4-week package, which is what he typically provides. The participant was asked to prepare the order as stated on the original prescription. He verbalized that he would fill two 4-week cartons and the steps that he would take in order to do that. After being reminded by the moderator that he could use the pharmacy shelf in the room, he stated that he had forgotten that the pharmacy shelf was there. | Artifact of Simulated Environment
Due to unfamiliarity with the test environment, the participant forgot about the pharmacy shelf in the test room. The participant immediately noticed that the NDC on the label and carton did not match. Without realizing that there was a pharmacy shelf available, he proceeded to correct the prescription to align with the materials he had available to him (see secondary cause analysis). The participant noticed the correct carton on the shelf only after the moderator reminded him that he was free to utilize the shelf provided. He then correctly filled the prescription with the 8-week carton.

Negative Transfer
While the participant correctly identified the medication name and strength, and recognized that the quantity and NDC were incorrect, he assumed that the
| Pharmacist needs to identify incorrectly filled “NextGen” prescription order and correct it | 1 | Observed
The participant approved one Viekira XR carton instead of one “NextGen 8-Week” carton.  

Participant Explanation of Failure
The participant explained that he overlooked the name of the medication on the carton and the strength, and was more focused on confirming the correct quantity of the medication. He also explained that the format of the medication quantity on the label (Quantity Filled: 168 of 168) was confusing to him. Although he knew that one carton of Viekira XR contained 84 tablets, the participant assumed that the order he was reviewing was the final (second) refill of the medication. He explained that on the label that he uses at work, the quantity is specified as “Quantity: 168”. Additionally, the participant stated that all staff at his workplace use scanners when filling and verifying the prescription orders. If the NDC does not match, the pharmacist returns the order to the technician for correction. **Patient Inattentiveness**
When describing his typical process at work, the participant explained that he verifies that the medication name and NDC are correct on the prescription, label, and medication carton. While the participant stated that he did compare the medication name from the prescription to the label, he did not check the name or the NDC on the carton, despite this being his usual process. Inattentiveness to his typical procedure caused him to overlook the error. Additionally, he explained that he was confused about the format of the test label regarding the quantity of medication filled and was therefore overly focused on determining the quantity.

| Pharmacist needs to identify incorrectly filled “NextGen” prescription order and correct it. | 1 | Observed
The participant initially filled two “NextGen 4-Week” cartons, but was able to recover and correctly fill one “NextGen 8-Week” carton.  

Participant Explanation of Close Call
The participant immediately recognized the incorrectly filled prescription order. She stated that the order was for 8 weeks’ worth of treatment and the order she was reviewing contained only 4 weeks of treatment. She initially assumed she needed to add one more carton of the 4-week “NextGen” treatment to make it a 2-month supply, **Negative Transfer**
The participant understood that the order called for an 8-week supply of medication. She assumed that she just needed to add one more carton of “NextGen” 4-week supply, and did not expect there to be a separate carton containing an 8-week supply. Thus, her initial reaction was simply to double the 1-monly supply in order to make it a 2-month supply,
make it an 8-week supply. Once she pulled the second 4-week “NextGen” carton from the shelf, she proceeded to compare the NDC on the medication label and the cartons. She caught the discrepancy between the NDCs on the packages and medication label. The participant then returned the 4-week cartons and successfully selected the 8-week “NextGen” carton from the shelf.

We have provided several images below to illustrate the similarities between the NextGen 4-Week and NextGen 8-Week.

![Pharmacy shelf with “NextGen 4-Week,” “NextGen 8-week,” Technivie, and Viekira XR.](image1)

![“NextGen 4-Week” carton](image2)

![“NextGen 8-Week” carton](image3)

We note AbbVie did not provide any additional mitigation for the carton based on the observed failures during the study. AbbVie determined policies and procedures used in a specialty pharmacy such as pharmacist verification, barcode scanning, and ePrescribing to significantly reduce the likelihood of the failures described in Table 3 going unnoticed. Regarding error related to “NextGen 4-Week” and “NextGen 8-Week” quantity, AbbVie acknowledges that if a failure is not corrected it could result in wrong treatment duration errors but did not offer any additional mitigation strategies for this type of failure.

We acknowledge the error where one pharmacist incorrectly verified Viekira XR instead of correcting to “NextGen 8-Week” and agree with AbbVie that barcode scanning reduces the likelihood that this type of error would go unnoticed. Additionally, we determined the Viekira XR and the “NextGen” cartons are sufficiently distinguishable from one another; however, based on other failures observed during this session of the HF study, we determined that selection error between the 4-Week and the 8-Week “NextGen” cartons has not been fully addressed.

We provide recommendations 1 through 4 for carton revisions to AbbVie in letter ready format in section 4.2 (see recommendations stated in section 3.1.1 under Prescription Fill Task Failures).
3.1.2 Content Statement Knowledge Task

The second part of the HF label comprehension validation study was conducted to evaluate user comprehension of the medication content statement on the “NextGen 8-Week” carton and involved three user groups: pharmacists (n = 15), pharmacy technicians (n = 15), and HCV-infected patients (n = 15). Each participant was asked to identify the number of weeks’ and months’ worth of medication contained in the 8-week carton.

- 1 pharmacy technician of 45 total participants incorrectly stated that the 8-week glecaprevir/pibrentasvir carton contained 4 weeks of therapy.

The participant explained that she “quickly glanced” at the content statement and only noticed the portion stating “4 weekly cartons” and not the 8-Week statement on the PDP of the carton labeling as described in Table 15 of Appendix C.

AbbVie determined negative transfer as the root cause to the failure described above and AbbVie did not incorporate any additional mitigation. AbbVie determined that policies and procedures used in specialty pharmacy such as pharmacist verification, bar code scanning, and ePrescribing would significantly reduce the likelihood of this failure going unnoticed. We note that negative transfer is a type of known use related issue that should have been addressed as part of developing this product. As such, we determined the “NextGen” cartons can be revised to further mitigate errors of this nature going unnoticed and provide recommendation to AbbVie in letter-ready format in section 4.2 (see recommendations stated in section 3.1.1 under Prescription Fill Task Failures).

3.2 Container Labels and Carton Labeling

AbbVie stated the “NextGen” carton was fashioned after the Technivie and Viekira XR carton labeling; therefore, we evaluated the “NextGen” carton against the Technivie and Viekira XR cartons. We determined the “NextGen” carton is sufficiently differentiable from the Technivie and Viekira XR cartons based on the results observed in the HF label comprehension validation study and because the “NextGen” carton utilizes a different color scheme and graphic on the principal display panel (PDP) than Technivie and Viekira XR (see appendix G).

3.2.1 “NextGen” 4-Week and 8-Week Carton Labeling

The two proposed cartons utilize different graphics that aid in providing distinction between them. We find a “NextGen” 4-Week and 8-Week carton acceptable to co-exist on the market, but identified the following areas for improvement in additional to the recommendations stated in section 3.1.1:

1. A section designated for the expiration date and lot number is missing from the monthly carton labeling, 3ct daily wallet, and the expiration and lot numbers are required on the immediate container and carton labeling per 21 CFR 201.17 and 21 CFR 201.10(i)(1), respectively.
3.2.4 Technivie and Viekira XR vs glecaprevir/pibrentasvir Carton Labeling

The PDP of each product’s primary carton label is visually distinct from one another in graphic design and color scheme. The glecaprevir and pibrentasvir contains different active ingredients than Technivie and Viekira XR is not likely to be stored adjacent to either on a pharmacy shelf. We find this acceptable from a medication error perspective.

3.3 FULL PRESCRIBING INFORMATION (FPI)

We assessed the Dosage and Administration, Dosage Forms and Strengths, How Supplied/Storage and Handling, and Patient Counseling Information sections of the FPI and the Highlights of Prescribing Information and Patient Information for areas of vulnerability to medication errors. We identified the following areas for improvement:

1. Under section 2.2 of the Dosage and Administration section, paragraph 3 states that Tables 1 and 2 provide the recommended treatment duration based on patient populations, HCV mono-infected and HCV/HIV-1 co-infected. Tables 1 and 2, however, do not clearly define that the HCV/HIV-1 co-infected treatment population is included. For clarity, we recommend Table 1 and 2 be revised to state which treatment population, HCV mono-infected or HCV/HIV co-infected, corresponds to the treatment durations outlined in each table by defining in either the title of Tables 1 and 2 or by including HCV/HIV-1 co-infected in the treatment population column of each table, respectively.

2. Section 17 (Patient Counseling Information) is missing administration instructions to advise patients to . We recommend this information is added to be consistent with section 2.2 (Recommended Dosage in Adults) of the FPI and to mitigate wrong administration technique errors. We defer to DAVP to make the final determination on acceptability of the statements to for this product. If DAVP determines the statement is not necessary because the tablets are determined not to be a modified release formulation, it should be removed from section 2.2.
4 CONCLUSION & RECOMMENDATIONS

The human factors (HF) label comprehension validation study results show that the “NextGen 4-Week” and “NextGen 8-Week” carton labeling are sufficiently differentiable from the Technivie and Viekira XR carton labeling; however, the study results failed to show that the “NextGen 4-Week” and 8-week carton labeling are sufficiently differentiable from one another. Therefore, we provide recommendations to improve readability and provide additional visual cues to help in differentiating the “NextGen 4-Week” and 8-Week carton labeling to mitigate selection errors between the two carton labeling. These changes will not require additional validation through another HF validation study as the revisions are intended to offer clarity and would not significantly change the appearance of the carton labeling, nor do we believe the revisions would introduce new risks for medication errors. Lastly, we provide recommendations for the PI to clarify the intended treatment population in Tables 1 and 2 of the Dosage and Administration section and to include additional important instructions in the Patient Counseling section. We provide our recommendations to the Division in section 4.1 and to AbbVie in letter-ready format in section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Consider revising Tables 1 and 2 in the Dosage and Administration sections of the FPI to state which treatment population, HCV mono-infected or HCV/HIV-1 co-infected, corresponds to the treatment durations outlined in the each table by incorporating “HCV/HIV-1 co-infected” in either the title of each table or by defining in the treatment population column of each table, respectively, to provide clarity on the treatment population.

2. Section 17 (Patient Counseling Information) should be revised to include administration instructions to “We defer to DAVP to make the final determination on acceptability of the statements to “ for this product. If DAVP determines the statement is not necessary because the tablets are determined not to be a modified release formulation, it should be removed from section 2.2.

4.2 RECOMMENDATIONS FOR ABBVIE

The human factors (HF) label comprehension validation study results show that “NextGen 4-Week” and “NextGen 8-Week” carton labeling are not sufficiently differentiable from one another. Therefore, we propose the following recommendations to mitigate selection errors between the two cartons. These changes will not require additional validation through another HF validation study. The following recommendations need to be implemented prior to approval of this NDA:
**Carton Labeling**

1. We are concerned the “8-WEEK” statement located on the outermost carton labeling may be misinterpreted by patients as the full therapy duration and subsequently take the medication for 8 weeks only when intended therapy duration is 12 or 16 weeks. Consider revising “8-WEEK” to state “8-WEEK SUPPLY (168 tablets).”

2. Include a similar statement (e.g. 4-WEEK SUPPLY (84 tablets)) on the “NextGen” 4-Week outermost carton labeling to provide an additional differentiating cue to users.

3. Enlarge the last two digits in the NDCs of the 4-week and 8-week cartons in a format such as xxxx-xxxx-XX to provide an additional visual cue to aid in differentiating the two cartons as both pharmacists and pharmacy technicians identified “checking NDCs” as a form of product verification during the HF validation study.

4. Consider duplicating the principle display panel of the 4-week and 8-week carton labeling to also appear on the top closure flap of each carton. To accommodate this placement, we recommend you move the area labeled as “Area for pharmacy label” on the top closure flap to the back panel of the carton labeling.

**Daily Dose Wallet Container Label**

5. A section for the expiration date and lot number has not been designated on the monthly carton labeling, 3ct daily wallet, The expiration date and lot number are required on the immediate container and carton labeling per 21 CFR 201.17 and 21 CFR 201.10(i)(1), respectively. Ensure the final container labels and carton labeling contains the lot number and expiration date.
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for glecaprevir and pibrentasvir tablet submitted by AbbVie on December 14, 2016.

| Table 2. Relevant Product Information for glecaprevir and pibrentasvir tablet |
|-------------------------------|---------------------------------|
| **Initial Approval Date**     | N/A                             |
| **Active Ingredient**         | glecaprevir and pibrentasvir    |
| **Indication**                | Treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection |
| **Route of Administration**   | Oral                            |
| **Dosage Form**               | Film-coated tablet             |
| **Strength**                  | 100 mg/ 40 mg                   |
| **Dose and Frequency**        | 3 tablets (300 mg/ 120 mg) once daily |
| **How Supplied**              | Will be available in both a monthly (4-week) and 8-week carton. Each 8-Week carton will contain two monthly cartons. Each monthly carton will contain 4 weekly cartons. Each weekly carton will contain 7 daily dose wallets. Each daily dose wallet will contain three 100 mg glecaprevir/40 mg pibrentasvir tablets. |
| **Storage**                   | Store at or below 30°C (86°F)   |
| **Container Closure**         | Child-resistant blister packs  |
APPENDIX C. HUMAN FACTORS STUDY

C.1 STUDY DESIGN

C.1.1 OBJECTIVES

- PHARMACY DIFFERENTIATION STUDY: to assess users’ ability to differentiate the new AbbVie HCV “NextGen 8-Week” carton from three other AbbVie HCV cartons presented on a typical pharmacy shelf when filling and/or reviewing prescription orders.

- CONTENT STATEMENT KNOWLEDGE TASK STUDY: to evaluate user comprehension of medication content statement on the HCV “NextGen 8-Week” carton during a knowledge task. This task also aimed to determine the extent to which information on the outer carton was findable.

C.1.2 PARTICIPANTS

PHARMACY DIFFERENTIATION STUDY

- 15 pharmacists
- 15 pharmacy technicians

Table 3. Demographic Information summary - pharmacy technicians & pharmacists

<table>
<thead>
<tr>
<th>Participant Group – Pharmacy</th>
<th>Number of Participants, Total N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>18-25</td>
<td>1</td>
</tr>
<tr>
<td>26-45</td>
<td>27</td>
</tr>
<tr>
<td>46-55</td>
<td>2</td>
</tr>
<tr>
<td>56-65</td>
<td>0</td>
</tr>
<tr>
<td>Pharmacy type</td>
<td></td>
</tr>
<tr>
<td>Specialty</td>
<td>12</td>
</tr>
<tr>
<td>Retail</td>
<td>7</td>
</tr>
<tr>
<td>Home infusion</td>
<td>4</td>
</tr>
<tr>
<td>Hospital</td>
<td>4</td>
</tr>
<tr>
<td>Compound</td>
<td>1</td>
</tr>
<tr>
<td>Geriatric</td>
<td>1</td>
</tr>
<tr>
<td>Independent</td>
<td>1</td>
</tr>
<tr>
<td>Years of experience in the field</td>
<td></td>
</tr>
<tr>
<td>5 to 10</td>
<td>11</td>
</tr>
<tr>
<td>10+</td>
<td>19</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>8</td>
</tr>
<tr>
<td>College (Bachelor’s Degree)</td>
<td>9</td>
</tr>
<tr>
<td>Master’s or Doctoral Degree (PharmD)</td>
<td></td>
</tr>
</tbody>
</table>
KNOWLEDGE TASK STUDY

- 15 pharmacists (same from differentiation study)
- 15 pharmacy technicians (same from differentiation study)
- 15 HCV-infected patients

Table 4. Demographic information summary - HCV patients

<table>
<thead>
<tr>
<th>Participant Group – HCV Patients</th>
<th>Number of Participants, total N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>18-25</td>
<td>1</td>
</tr>
<tr>
<td>26-45</td>
<td>7</td>
</tr>
<tr>
<td>46-55</td>
<td>5</td>
</tr>
<tr>
<td>56-65</td>
<td>2</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>6</td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
</tr>
<tr>
<td>Mix</td>
<td>1</td>
</tr>
<tr>
<td>Income</td>
<td></td>
</tr>
<tr>
<td>Less than 30K</td>
<td>2</td>
</tr>
<tr>
<td>30K-50K</td>
<td>4</td>
</tr>
<tr>
<td>50K-75K</td>
<td>2</td>
</tr>
<tr>
<td>75K-100K</td>
<td>5</td>
</tr>
<tr>
<td>100K+</td>
<td>2</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>High School (Some college)</td>
<td>8</td>
</tr>
<tr>
<td>College (Bachelor’s Degree)</td>
<td>7</td>
</tr>
</tbody>
</table>

C.1.3 TESTING ENVIRONMENT

The study was conducted at two usability-testing facilities in [text obscured]. The test rooms in both locations were set up to mimic an actual pharmacy and the setup was identical for pharmacist and pharmacy technician participants.
C.1.4 STUDY SESSION DESCRIPTION/TASKS

C.1.4.1. Pharmacy Differentiation Study

The following materials were available to pharmacists and pharmacy technician participants:

- Pharmacy shelves with medication cartons
- Bin for filled prescriptions
- Bags and stapler for filling prescriptions
- Prescription forms (electronic and paper) and labels
- Paper, pen and calculator

Each session was recorded and captured the following:

- Overhead shot of the participant interacting with the stimuli
- A face shot of the participant
- A shot of the participant interacting with the pharmacy shelves
- A screen-share of the participant’s computer
- Session information
- Audio of the moderator and participant

Pharmacy technicians were tasked with filling four different prescription orders, during which they were asked to select the correct medication carton from a simulated pharmacy shelf (see Figures 1 through 5) based on information provided in an electronic prescription order and a printed prescription label. Pharmacy technicians were then asked to prepare the selected medication carton to be sent to a pharmacist for review.

Each pharmacist was asked to verify four different pre-filled prescription orders, including one incorrectly filled order. The pharmacists were expected to identify an incorrectly filled order and then correct it by selecting the correct medication carton from a pharmacy shelf. An electronic prescription order and a printed prescription label were provided for each task. Once they reviewed the order, they were asked to prepare the order to be sent to a hypothetical patient.

All pharmacy technician and pharmacist sessions were run independently from each other. Participants were not given time to familiarize themselves with the supplied medication cartons prior to the start of the study.
and Viekira XR.

Figure 4. Technivie carton

Figure 5. Viekira XR carton

Figure 6. Lab setup
Figure 7. Sample of an electronic prescription order for NextGen 8-Week supply
C.1.4.2. Content Statement Knowledge Task Study

Aimed at assessing the key pieces of information on the outer carton:

- How many months’ worth of medication are contained in a NextGen 8-Week carton
- How many weeks’ worth of medication are contained in a NextGen 8-Week carton

The sessions for the pharmacy technicians and pharmacists were conducted after the prescription fill/verification tasks, after the participants interacted with all four medication cartons.

To assess the completeness and comprehensiveness of the content statement on the outer carton alone, the patient sessions utilized a directed use approach: all patient participants were asked to provide answers while strictly relying on the information on the outer carton and were discouraged from opening the carton and interacting with its contents.
on closure flap of the carton

C.1.5 CRITICAL TASK EVALUATED DURING THE SESSIONS

C.1.5.1 Pharmacy Differentiation Study

Pharmacy Technicians

<table>
<thead>
<tr>
<th>Success</th>
<th>Accurate prescription fill was determined by the moderator. Once the participant placed a filled prescription bag into the bin to indicate s/he was done with the task, the moderator examined a filled bag to ensure the prescription matched the product inside.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close Call</td>
<td>By definition, a close call is any instance of potential failure that is avoided by vigilance on the part of the user. Thus, a close call would pose no risk to the patient because the prescription error would be identified and corrected prior to reaching the patient. A filling task was marked a close call in the event a pharmacy technician first selected an incorrect medication carton, but self-corrected before indicating s/he was done with the task.</td>
</tr>
<tr>
<td>Failure</td>
<td>A filling task was marked a failure if a pharmacy technician finalized the prescription by including the incorrect medication carton in the bag and indicated it was ready to be sent to the pharmacist.</td>
</tr>
</tbody>
</table>
Pharmacists

<table>
<thead>
<tr>
<th>Success</th>
<th>Accurate prescription filling verification was determined by the moderator who examined a filled bag to ensure the prescription matches the product inside. To qualify as a success, the pharmacist needed to check the correctly filled prescription, and indicate that it was ready to be sent to the patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close Call</td>
<td>A verification task was marked a close call in the event a pharmacist was about to finalize an incorrectly filled bag, but self-corrected before indicating s/he was done with the task.</td>
</tr>
<tr>
<td>Failure</td>
<td>A verification tasks was marked a failure if a pharmacist finalized the prescription by including the incorrect medication in the bag and indicated it was ready to be sent to the patient.</td>
</tr>
</tbody>
</table>

A deep-dive analysis was conducted in all instances of close calls and failures. When necessary to gain complete understanding of root cause, the moderator asked a participant to walk through the task once more, but this time s/he was instructed to use a think-aloud protocol. The second walkthrough did not affect the original scoring of participant success/close all/failure.

C.1.5.2. Content Statement Knowledge Task Study

All participants (Pharmacists, Pharmacy Technicians, HCV Patients)

<table>
<thead>
<tr>
<th>Success</th>
<th>Located and correctly interpreted the content statement on the NextGen 8-Week outer carton.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td>Did not locate and/or did not correctly interpret the content statement on the NextGen 8-Week outer carton.</td>
</tr>
</tbody>
</table>

A deep-dive analysis was conducted in all instances of failures. When necessary to gain complete understanding of root cause, the moderator asked a participant to walk through the task once more. The participants were asked to show were they found content statement on the outer carton and explain in detail how they understood that piece of the content statement. The second walkthrough did not affect the original scoring of participant success/failure.
C.2 Results

C.2.1 Pharmacy Differentiation Tasks

All participants’ failures were attributed to a negative transfer of training from the participants’ usual work environment, artifact of simulated use, slip/lapse, and participants’ inattentiveness. A large majority of participants reported that the standard procedure at their workplace involves using scanners to prevent the types of failures observed in this study (i.e. failure to manually check product NDC). Scanners are used to scan the barcode on the medication carton or container and prescription label to verify that the correct medication product is pulled off the shelf. Scanners are largely used by both pharmacy technicians and pharmacists during the filling and verification processes. The feedback collected from participants suggests that many ultimately rely on scanners to verify the product.

Participants also explained that if the scanner notifies them about an incorrect product, the product is returned to the filling station for review and correction. A few pharmacists expressed surprise that an incorrect order was sent to the reviewing station at all because in real life work situations, multiple checkpoints are in place to ensure that an order is correct before being sent to the pharmacist; thus, the possibility of an incorrect medication being sent to the patient is very low.

For pharmacy technicians and pharmacists, a lack of familiarity with some or all medication cartons and the simulated labels presented in this study factored into some errors. However, the results show no patterns of preventable use errors that present an unacceptable risk of harm to patients. Additionally, based on the feedback received from the participants, any discrepancies between cartons and medication labels are likely to be caught prior to dispensing in real-world scenarios (e.g. by the use of scanners). Based on known standard processes and those shared by the pharmacists, if the observed errors occurred in real-life scenarios, the likelihood of any risk to the patient would be low.

Below is a summary of participant performance on pharmacy differentiation tasks across pharmacy technician and pharmacist participants

Table 5. Success, close call, and failure rates by task - pharmacy technicians
Table 6. Success, close call, and failure rates by task - pharmacists

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Task</th>
<th>Cartons presented for order verification</th>
<th>Task Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacist, N=15</td>
<td>Verifiction task - verify and confirm a filled prescription order</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NexGen 4-week - Correctly-filled order task</td>
<td>9 of 15 (60%)</td>
<td>0 of 15</td>
</tr>
<tr>
<td></td>
<td>NexGen 4-week - Incorrectly-filled order task</td>
<td>2 of 6 (33.3%)</td>
<td>1 of 6 (16.7%)</td>
</tr>
<tr>
<td></td>
<td>NexGen 5-week - Correctly-filled order task</td>
<td>15 of 15 (100%)</td>
<td>0 of 15</td>
</tr>
<tr>
<td></td>
<td>Technique - Correctly-filled order task</td>
<td>11 of 11 (100%)</td>
<td>0 of 11</td>
</tr>
<tr>
<td></td>
<td>Technique - Incorrectly-filled order task</td>
<td>4 of 4 (100%)</td>
<td>0 of 4</td>
</tr>
<tr>
<td></td>
<td>Vistar XR - Correctly-filled order task</td>
<td>10 of 10 (100%)</td>
<td>0 of 10</td>
</tr>
<tr>
<td></td>
<td>Vistar XR - Incorrectly-filled order task</td>
<td>4 of 5 (80%)</td>
<td>0 of 5</td>
</tr>
</tbody>
</table>

Table 7. Individual task performance - pharmacy technicians

<table>
<thead>
<tr>
<th>Pt</th>
<th>NexGen 4-week Task</th>
<th>NexGen 5-week Task</th>
<th>Technique Task</th>
<th>Vistar XR Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT001</td>
<td>Failure - (Drug)</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT002</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT003</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT004</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT005</td>
<td>Failure - (Ambot)</td>
<td>Failure - (Ambot)</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT006</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT007</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT008</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT009</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT010</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT011</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT012</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT013</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT014</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT015</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT016</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT017</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>PT018</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
</tbody>
</table>
Table 8. Individual task performance (correctly-filled order tasks) - pharmacists

<table>
<thead>
<tr>
<th>Task</th>
<th>NextGen 4-week</th>
<th>NextGen 8-week</th>
<th>Technico carton</th>
<th>Visaera XR carton</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0001</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0002</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0003</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0004</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0005</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0006</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0007</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0008</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0009</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0010</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0011</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0012</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0013</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0014</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0015</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0016</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
</tbody>
</table>

1 Grey cells signify those tasks that were given to pharmacists representing incorrectly filled prescriptions as part of the simulation

Table 9. Individual task performance (incorrectly-filled order task) - pharmacists

<table>
<thead>
<tr>
<th>Task</th>
<th>NextGen 4-week</th>
<th>NextGen 8-week</th>
<th>Technico carton</th>
<th>Visaera XR carton</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0001</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0002</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0003</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0004</td>
<td>Failure</td>
<td>Close Call -</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0005</td>
<td>Failure</td>
<td>Close Call -</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0006</td>
<td>Failure</td>
<td>Close Call -</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0007</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0008</td>
<td>Failure</td>
<td>Close Call -</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0009</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0010</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0011</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0012</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0013</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0014</td>
<td>Failure</td>
<td>Close Call -</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0015</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>P0016</td>
<td>Failure</td>
<td>Close Call -</td>
<td>Success</td>
<td>Success</td>
</tr>
</tbody>
</table>

2 Grey cells signify those tasks that were given to pharmacists representing correctly filled prescriptions as part of the simulation

Table 10. Disqualified Participant List

<table>
<thead>
<tr>
<th>Participant #</th>
<th>Participant Group</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>P007</td>
<td>Pharmacy technician</td>
<td>The participant reported to be working at a specialty infusion pharmacy and interacting only with insulin drugs and never with medications that come in cartons that contain tablets.</td>
</tr>
<tr>
<td>P001</td>
<td>Pharmacy technician</td>
<td>The participant reported that she works at a long-term care pharmacy. Even though she worked at a specialty unit within a hospital pharmacy, she did not fill medication cartons for inpatient care.</td>
</tr>
<tr>
<td>P001</td>
<td>Pharmacist</td>
<td>The participant works at a long-term care pharmacy setting where the medications are dispensed in bubble packs. The pharmacy does not stock or dispose medications that come in cartons.</td>
</tr>
</tbody>
</table>

Reference ID: 4097911
## Failure Analysis

### Table 11. Pharmacy differentiation failure discussion table - pharmacy technicians

<table>
<thead>
<tr>
<th>Participant</th>
<th>PT601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Description</td>
<td>Pharmacy Technician Male NVC of 4/6</td>
</tr>
<tr>
<td><strong>Stop Failure</strong></td>
<td>Participant filled one monthly carton and one weekly carton from the NestGen 8-week carton instead of one NestGen 4-week carton.</td>
</tr>
<tr>
<td><strong>Observed Behavior</strong></td>
<td>The participant was given a prescription order and a matching prescription label for NestGen 4-week carton. The participant pulled NestGen 8-week carton off the shelf, removed one NestGen 4-week carton from inside of the 8-week carton, plus one weekly carton from the second 4-week carton. The participant filled a total of 5 weeks’ worth of medication from NestGen 8-week carton.</td>
</tr>
<tr>
<td><strong>Participant Explanation</strong></td>
<td>At the beginning of the root cause discussion, the participant realized that he had selected an incorrect medication carton (NestGen 4-week instead of NestGen 8-week). He realized that the NDC on the medication label and the carton that he selected did not match. The participant explained that during the task he had relied solely on the medication names and strength when selecting the carton from the shelf, and did not crosscheck the NDC on the carton and medication label. He then explained that the standard practice at his workplace does involve checking the NDC, but during the task he only checked the medication names and the strength. He explained that during the prescription filling process at his pharmacy, a prescription is checked by more than one technician and/or pharmacist before the medication gets sent out to the patient. The participant also explained that his confusion around the medication quantity was due to his unfamiliarity with medications that are packaged as cartons. At his pharmacy, tablets are dispensed in bottles or blister cards as monthly supplies of 30 days. The pharmacy also typically repackages the products they receive from manufacturers, following the 30-day supply regimen of dispensing medications to patients. When he was tasked to dispense one month’s supply, he assumed he had to dispense at least 90 tablets, following the regimen of 3 tablets per day, according to NestGen 4-week prescription order. He stated that at his pharmacy, there are certain medications that come from the manufacturer in packaging that they are not allowed to open. In those cases, they are told to calculate the number of tablets needed for a 30 day supply and then dispense that amount or more. If they are not able to get the exact amount. This confusion led him to dispense 5 weekly cartons (105 tablets total, greater than 90 tablets) of NestGen instead of 4 weekly cartons (84 tablets).</td>
</tr>
<tr>
<td><strong>Root-Cause Analysis</strong></td>
<td>Silly Logic The participant’s instructions were correct to check the NDC, but when completing the simulated task, this was not done. This resulted in him pulling an 8-week NestGen carton rather than the 4-week carton. Negative Transfer The participant applied the training from his workplace, where the pharmacy staff dispenses medications only in multiples of 36 tablets without consideration of the pre-packaged, weekly quantities that are available in cartons. The participant made the assumption, based on the training from his workplace, that the “one month” of supply translated to 30 days, and then calculated the corresponding total tablet quantity by multiplying that by the number of tablets to be taken per day, giving him a quantity of 90 tablets rather than the prescribed amount of 84 tablets. The participant applied additional training that it is not permissible to break tamper-resistant packages. This led him to dispense the smallest possible amount of tablets greater than 90 (105 tablets = 5 weekly cartons).</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Even though the participant selected an incorrect medication carton, he selected the correct medication name and strength and filled a sufficient quantity of medication for a 4-week treatment plus one additional week. With the proposed treatment regimen for specific types of patient population being 8, 12, or 16 weeks, this error could potentially cause a patient to receive one week of supply more than the proposed dosing duration. At a maximum, a patient prescribed 16 weeks of treatment could be given 17 weeks of treatment. Although clinical studies have not evaluated durations greater than 16 weeks, one extra week of treatment is not expected to pose additional risks to the patient. Moreover, the observation that the safety profile is similar across the proposed dosing duration of 8, 12, and 16 weeks suggests that an extra week of dosing of Glucophage and Metformin will likely not impact the safety of the regimen. Policies and procedures used in a specialty pharmacy such as pharmacist verification, bar code scanning, and ePrescribing would significantly reduce the likelihood of this failure going unnoticed.</td>
</tr>
<tr>
<td><strong>Note</strong></td>
<td>The participant was recruited as a specialty pharmacy technician. During the warm-up questions at the beginning of the session, he reported that he works at a specialty oncologic pharmacy, and his primary responsibility is data entry.</td>
</tr>
</tbody>
</table>
Table 12. Pharmacy differentiation failure discussion table - pharmacists

<table>
<thead>
<tr>
<th>Participant</th>
<th>PT008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Description</td>
<td>Pharmacist</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>NVE of 6/6</td>
<td></td>
</tr>
<tr>
<td>Step Failure</td>
<td>Participant filled two NexGen 4-week cartons instead of one NexGen 8-week carton.</td>
</tr>
<tr>
<td>Observed Behavior</td>
<td>Participant reviewed the prescription form and label. She then walked to the pharmacy shelf with the label in hand and pulled one NexGen 4-week carton.</td>
</tr>
<tr>
<td>Participant Explanation</td>
<td>During root cause discussion, the participant realized she filled an incorrect carton because she was supposed to fill 2 months’ worth of therapy (according to the prescription), but filled only 1 month’s supply. She explained that during the task she was looking for medication quantity on the prescription order and the medication label, but was unable to find it. The participant explained that the medication quantity on the labels at her workplace is specified next to the name of the medication, as opposed to the upper right hand corner in the mock medication labels used as part of the study setup. The participant explained she was unable to compute the required quantity to be filled with the medication quantity in the carton that she selected. She also stated that she only checked the medication name when selecting the carton, and overlooked the NDC. The participant explained that she typically checks the NDC at week, but not checking it during the session was an oversight error. I just saw the name of the medication on the 4-week carton and the size of the box.</td>
</tr>
<tr>
<td>Root-Cause Analysis</td>
<td><strong>Negative Transfer:</strong> Due to participant’s inability to find the required medication quantity on the label, she was unable to confirm whether she selected the correct carton. Negative transfer of learning regarding identification of critical information from a pharmacy-generated label led to failure when using the simulated pharmacy label provided in the study.</td>
</tr>
<tr>
<td>Outcome</td>
<td>The participant selected the correct medication name and strength, but filled an insufficient quantity of medication. If this failure was not corrected, the patient would receive the correct medication but not the full treatment duration. If the patient did not realize that they had not received the full treatment duration, they will likely not reach sustained viral response. Policies and procedures used in a specialty pharmacy such as pharmacist verification, bar code scanning, and ePrescribing would significantly reduce the likelihood of this failure going unnoticed.</td>
</tr>
</tbody>
</table>

Table 12. Pharmacy differentiation failure discussion table - pharmacists
<table>
<thead>
<tr>
<th>Participant</th>
<th>PH008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Description</td>
<td>Pharmacist</td>
</tr>
<tr>
<td>Step Failure</td>
<td>The participant verified a filled prescription containing one NexGen 4-week carton instead of a NexGen 8-week carton as stated on the prescription order.</td>
</tr>
<tr>
<td>Observed Behavior</td>
<td>The participant compared the prescription order and the label. He then inspected the contents of the filled carton and incorrectly approved it to be sent to the patient.</td>
</tr>
<tr>
<td>Participant Explanation</td>
<td>During the task follow-up questions, the participant stated there was a mismatch between the NDCs on the medication label and on the carton, which caused him to be concerned. But, he stated he had opened the carton and verified that the weekly cartons contained the correct medication name, strength, and quantity. He said that these all matched, even though the quantity was in fact different, and then still proceeded to approve the incorrectly filled order. During later root cause discussion, the participant explained that he made a mistake when checking the quantity of the medication. &quot;It was a computational error. I thought it was correct for a quantity of 158 tablets. Purely a human error.&quot; Later in the study session, he said that at his workplace, the staff typically uses a scanner when filling and verifying prescriptions. The participant explained that if the scanner notifies them about a wrong product, the staff will then check the medication name, strength, and quantity inside the package. If all three items match the label, the staff is allowed to override the prescription order and approve the product, despite a mismatched NDC.</td>
</tr>
<tr>
<td>Root-Cause Analysis</td>
<td>Slip/Lapse</td>
</tr>
<tr>
<td>Outcome</td>
<td>The participant reported that his pharmacy has procedures to validate the prescription approval process. Despite the fact that he followed this procedure, a computational error resulted in verification of an incorrect prescription. If this failure was not corrected, the patient would receive the correct medication but not the full treatment duration. If the patient did not realize that they had not received the full treatment duration, they would likely not reach sustained T2R response.</td>
</tr>
<tr>
<td>Participant Description</td>
<td>FH014</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------</td>
</tr>
</tbody>
</table>

### Step Failure
Participant forgot that simulated pharmacy shelf was available and did not attempt to remove the correct prescription. He reversed the insurance claim to fill 4 weeks instead of 8 weeks.

### Observed Behavior
Participant reviewed the prescription order, the label, and the carton. He immediately noticed that the NDC on the label did not match the NDC on the carton. He then explained that he needed to fill two cartons of NextGen 4-week in order to fill 168 tablets of NextGen. He then stated that he assumed that insurance would cover 2 cartons and verbalized the steps that he would take to reverse the claim and only dispense a 4-week supply. When asked to follow the prescription as written, the participant indicated that he would dispense two 4-week cartons and change the NDC on the label. The moderator then reminded the participant that the pharmacy shelf in the room was available to be used during the simulated task. The participant stated that he had forgotten about the simulated pharmacy shelf. The participant approached the pharmacy shelf and immediately noticed NextGen 8-week carton. He then pulled one NextGen 8-week carton and successfully corrected the order.

### Participant Explanation
Participant reviewed an incorrectly filled carton, the label, and the prescription form. He immediately noticed that the NDC on the carton did not match the label. He understood that the order was filled incorrectly, and that the quantity needed to be filled was 168 tablets, and that the filled carton (NextGen 4-week) contained only 44 tablets. He also explained that he would correct the NDC on the label to match the NDC of a 4-week carton, and fill two cartons of a NextGen 4-week supply. The participant explained that the label he was given was incorrect since the NDC on the label did not match the NDC on the 4-week carton. He stated that he would reverse the insurance claim for the 8-week package and reprocess for the 4-week package, which is what he typically provides. The participant was asked to prepare the order as stated on the original prescription. He verbalized that he would fill two 4-week cartons and the steps that he would take in order to do that. After being reminded by the moderator that he could use the pharmacy shelf in the room, he noted that he had forgotten that the pharmacy shelf was there. He then matched the NDC on the 8-week carton and the label, and realized that that was the carton that needed to be filled. The participant cross-checked the NDCs on the carton and the label once again, checked the correct medication quantity in the 8-week carton, and successfully filled one NextGen 8-week carton.

### Root-Cause Analysis
**Artifact of simulated environment**
Due to unfamiliarity with the test environment, the participant forgot about the pharmacy shelf in the test room. The participant immediately noticed that the NDC on the label and carton did not match. Without realizing that there was a pharmacy shelf available, he proceeded to correct the prescription to sign with the medications he had available to him (see secondary cause analysis). The participant noticed the correct carton on the shelf only after he was reminded by the moderator that he was free to utilize the shelf provided. He then correctly filled the prescription with the 8-week carton.

### Secondary Cause Analysis
**Negative Transfer**
While the participant correctly identified the medication name and strength, and recognized that the quantity and NDC were incorrect, he assumed that the discrepancy was due to the patient’s insurance rejecting the claim. As a result, he chose to ignore the label to reflect one 4-week prescription with a second 4-week refill. When asked to fill the original prescription, the participant first indicated that he would dispense two 4-week cartons, but then self-corrected to dispense one 8-week carton after being reminded that he could utilize the simulated pharmacy shelf.

### Outcome
Even if the participant had reversed the insurance claim to fill two separate 4-week prescriptions, or had filled the prescription using two 4-week packages, the patient would have received the correct medication, strength, and quantity. Therefore, there would be no risk to the patient. Policies and procedures used in a specialty pharmacy such as pharmacist verification, bar code scanning, and ePrescribing would significantly reduce the likelihood of this failure going unnoticed.
<table>
<thead>
<tr>
<th>Participant</th>
<th>FH010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant Description</strong></td>
<td>Pharmacist Male N/V: 6/6</td>
</tr>
<tr>
<td><strong>Step Failure</strong></td>
<td>The participant approved one Viokalin XR carton instead of one NextGen 1-week carton.</td>
</tr>
<tr>
<td><strong>Observed Behavior</strong></td>
<td>The participant compared the prescription order and the label, removed a Viokalin XR carton from the bag, checked its contents and placed the carton back into the medication bag and placed the bag into the bin. In follow-up questioning, the participant stated that after he placed the medication bag into the bin, he noticed that the NDC was incorrect. The participant stated that the label was incorrect because the NDC number listed did not match the drug that was being dispensed.</td>
</tr>
<tr>
<td><strong>Participant Explanation</strong></td>
<td>The participant explained that he overlooked the name of the medication on the carton and the strength, and was more focused on confirming the correct quantity of the medication. He also explained that the format of the medication quantity on the label (Qty Filled: 105 of 160) was confusing to him. Although he knew that one carton of Viokalin XR contained 81 tablets, the participant assumed that the order he was reviewing was the final (second) refill of the medication. He explained that on the label that he used at work, the quantity is specified as “Quantity: 160.” Additionally, the participant stated that all staff at his workplace use scanners when filling and verifying the prescription orders. If the NDC does not match, the pharmacist returns the order to the technician for correction.</td>
</tr>
<tr>
<td><strong>Root-Cause Analysis</strong></td>
<td>When describing his typical process at work, the participant explained that he verifies that the medication name and NDC are correct on the prescription, label and medication carton. While the participant stated that he did compare the medication name from the prescription to the label, he did not check the name or the NDC on the carton, despite being his usual process. Inconsistencies in his typical procedure caused him to overlook the error. Additionally, he explained that he was confused about the format of the carton label regarding the quantity of medication filled and was therefore overly focused on determining the quantity.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>The participant verified the incorrect medication name, strength, and quantity. If this failure was not corrected, the patient would receive the incorrect medication and an incomplete treatment duration. If the patient did not realize that they had not received the full treatment duration, they will likely not reach sustained viral response. Policies and procedures used in a specialty pharmacy such as pharmacist verification, bar code scanning, and e-prescribing would significantly reduce the likelihood of this failure going unnoticed.</td>
</tr>
</tbody>
</table>

Table 13. Close call discussion table - pharmacist
C.2.2 Content Statement Knowledge Task

One pharmacy technician (PT015) misread the content statement on the “NextGen 8-Week” outermost carton labeling and incorrectly reported that the 8-week carton contained one month’s worth of medication. AbbVie did not identify any clinical consequences to this failure type. All patient and pharmacist participants successfully located the content statement information and interpreted it correctly.

Table 14. Content Statement Knowledge Task Results - pharmacy technicians, pharmacists, and patients

<table>
<thead>
<tr>
<th>Content Statement on HCV NextGen 8-week carton</th>
<th>Participant Group</th>
<th>Located answer, N of participants</th>
<th>Comprehended answer, N of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many months’ worth of medication are contained in this carton?</td>
<td>Pharmacy technicians</td>
<td>15 of 15 (100%)</td>
<td>15 of 15 (100%)</td>
</tr>
<tr>
<td></td>
<td>Pharmacists</td>
<td>15 of 15 (100%)</td>
<td>15 of 15 (100%)</td>
</tr>
<tr>
<td></td>
<td>HCV patients</td>
<td>15 of 15 (100%)</td>
<td>15 of 15 (100%)</td>
</tr>
<tr>
<td>How many weeks’ worth of medication are contained in this carton?</td>
<td>Pharmacy technicians</td>
<td>14 of 15 (93.3%)</td>
<td>14 of 15 (93.3%)</td>
</tr>
<tr>
<td></td>
<td>Pharmacists</td>
<td>15 of 15 (100%)</td>
<td>15 of 15 (100%)</td>
</tr>
<tr>
<td></td>
<td>HCV patients</td>
<td>15 of 15 (100%)</td>
<td>15 of 15 (100%)</td>
</tr>
</tbody>
</table>

Table 15. Table of Failure Discussion - pharmacy technician

<table>
<thead>
<tr>
<th>Participant</th>
<th>PT015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Description</td>
<td>Pharmacy Technician</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>NVS of 2/5</td>
<td>NVS of 2/5</td>
</tr>
<tr>
<td>Step Failure</td>
<td>The participant incorrectly stated that the 8-week carton contained 4 weeks’ worth of medication.</td>
</tr>
<tr>
<td>Observed Behavior</td>
<td>The content statement on the NextGen 8-week outer carton states “This 8-week carton contains 108 tablets packaged as follows: 2 monthly cartons of therapy. Each monthly carton contains 4 weekly cartons…” The participant correctly used the first part of the content statement to determine that there were 2 months of therapy in the carton. However, when asked how many weeks of medication were in the carton, he stated that there were 4 weeks, based on the second part of the statement. She appeared to be focused on the numerical values contained in the statement rather than the meaning of the full statement.</td>
</tr>
<tr>
<td>Participant Explanation</td>
<td>The participant explained that she “quickly glanced” at the content statement and only noticed the portion stating “4 weekly cartons” in the instruction. She stated that she did not notice the “8-WEED…” label on the upper flap or on the front side of the carton. The participant quickly recovered and explained that it was an oversight on her part.</td>
</tr>
<tr>
<td>Root Cause Analysis</td>
<td>Negative Transfer</td>
</tr>
<tr>
<td></td>
<td>The knowledge task questions request the quantity of months and weeks contained within the 8-week package. This participant appeared to be looking for numeric quantity values to answer both questions. As a result, it appeared that she passed over additional text that stated “each monthly carton contains” and only focused on “4 weekly cartons.” This can be attributed to a preconception on the participant’s part to focus on numeric quantity that led her to overlook the non-numeric part of the content statement.</td>
</tr>
<tr>
<td>Outcome</td>
<td>If the prescription had called for 8 weeks of medication and the pharmacy technician had incorrectly interpreted the content statement to mean that this package contained 4 weeks of medication, the technician may have filled the prescription with two 8-week cartons, and the patient would have received 16 weeks of medication, a duration which has been shown to be clinically safe. Despite this knowledge task error, the participant accurately filled prescriptions, including one 8-week prescription, during the simulated use portion of the study. Policies and procedures used in a specialty pharmacy such as pharmacy verification, bar code scanning, and prescribing would significantly reduce the likelihood of this failure going unnoticed.</td>
</tr>
</tbody>
</table>
APPENDIX F. WRITTEN RESPONSES, INFORMATION REQUESTS, AND EMAIL CORRESPONDENCE

- APRIL 8, 2016 WRITTEN RESPONSES TO ABBVIE’S FEBRUARY 29, 2016 MEETING REQUEST PACKAGE (IMAGES PERTAINING TO SECTION 2.1 HUMAN FACTORS INCLUDED)

This document can be found with signature date of 4/8/2016 in the AdminCorres section of the approval package.

2 Page(s) has been Withheld in Full because these are duplicate documents in AdminCorres section immediately following this page
April 6, 2017 email correspondence pertaining to daily wallet amendment submitted to NDA 209394 on April 13, 2017.

From: Gandhi, Virajkumar B  
Sent: Thursday, April 06, 2017 11:35 AM  
To: Moruf, Alicia  
Subject: NDA 209394 - Update to the outer panel of the G/P Daily Wallet

Dear Dr. Moruf,

AbbVie is proposing an update to the daily wallet pack front panel for G/P and would appreciate your feedback on the best approach to submit this change.

In the original NDA submitted on December 14, 2016, the front panel of the daily wallet pack is (b)(4) as identified on the left in below pictorial. AbbVie is proposing (b)(4) no other change is proposed to the daily wallet pack. I would appreciate if you could respond to the following questions regarding this update.

1. Could you kindly advise if AbbVie can submit this update to the daily wallet pack as an amendment to the NDA at this time or recommend that the change be submitted when comments are received on the draft carton and container labels? Please submit at this time.

2. At this point, AbbVie doesn’t have any physical samples of the proposed daily wallet pack. If FDA agrees to an amendment submission, AbbVie proposes to provide a graphical representation similar to what was submitted in the original NDA in Module 1, Section 1.14.1.1 (as attached). Does the FDA agree to this proposal? Yes we agree

3. Will the submission of the new proposal for daily wallet pack have any impact on the PDUFA date for the NDA? At this time, this amendment as described in this email, should have no impact on the PDUFA date.
Please let me know if you have any questions on the above proposal and perhaps we can have a brief call to further discuss.

Kind regards,

Viraj

VIRAJ GANDHI, MS MBA, RAC (US)
Senior Manager
Global Regulatory Strategy

abbvie

One North Waukegan Rd
Dept. PA72/Bldg. AP30-1
North Chicago, Illinois 60064

OFFICE: +1 847-938-1967
FAX: +1 847-935-5344

EMAIL: viraj.b.gandhi@abbvie.com

This communication may contain information that is proprietary, confidential, or exempt from disclosure. If you are not the intended recipient, please note that any other dissemination, distribution, use or copying of this communication is strictly prohibited. Anyone who receives this message in error should notify the sender immediately by telephone or by return e-mail and delete it from his or her computer.
APRIL 10, 2017 INFORMATION REQUEST PERTAINING TO LABELING AMENDMENT SUBMITTED TO NDA 209394 ON APRIL 17, 2017.

This document can be found with signature date of 4/10/2017 in the AdminCorres section of the approval package.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S WILSON
05/14/2017

OTTO L TOWNSEND
05/14/2017

QUYNNHUU T NGUYEN
05/15/2017
Clinical Inspection Summary

<table>
<thead>
<tr>
<th>Date</th>
<th>April 26, 2017</th>
</tr>
</thead>
</table>
| From       | Antoine El Hage, Ph.D. /OSI/DCCE/GCPAB  
Susan Thompson, M.D. /OSI/DCCE/GCPAB, Team Leader  
Kassa Ayalew, M.D., M.P.H. /OSI/DCCE/GCPAB, Branch Chief |
| To         | Alicia Moruf, Pharm.D., Regulatory Health Project Manager  
Lara Stabinski, M.D., Medical/Clinical Reviewer  
Wendy Carter, D.O. Team Leader/CTDL  
Division of Antiviral Products (DAVP) |
| NDA #      | NDA 209394     |
| Applicant  | AbbVie, Inc.   |
| Drug       | Glecaprevir/pibrentasavir-ABT-493+ABT-530 tablets |
| NME (Yes/No)| Yes            |
| Therapeutic Classification | Priority |
| Proposed Indication(s) | Treatment of chronic hepatitis C genotype 1-6 infected individuals |
| Consultation Request Date | January 17, 2017 |
| Summary Goal Date | July 14, 2017; Moved up to the first week of May, 2017 |
| Action Goal Date | August 14, 2017 |
| PDUFA Date  | August 14, 2017 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Papatheodoridos, Leroy, Ghalib, Felizarta, Lalezari, Bourgeois, Jazrawi, and Zogg were inspected in support of this NDA. The inspections of Drs. Jazrawi and Zogg revealed minor deviations that would not adversely impact data acceptability.

The pending classification of Dr. Zogg inspection is Voluntary Action Indicated (VAI), and the final classification of Jazrawi is Voluntary Action Indicated (VAI).

The inspection of the six remaining sites listed below revealed no regulatory violations. The pending classification of the six clinical sites (Papatheodoridos, Leroy, Ghalib, Felizarta, Lalezari, and Bourgeois) inspections was No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusion changes upon receipt and review of the EIRs.
The clinical studies inspected appear to have been conducted adequately. Overall, while the inspectional findings represent observed deficiencies, these findings are unlikely to have a significant impact on overall results. The data generated from all inspected sites appear acceptable for use in support of the respective indication.

Based on the inspections of the eight clinical sites, the inspectional findings support validity and acceptability of the data as reported by the sponsor under the pending application.

II. BACKGROUND

ABT-493 is an NS3/4A protein inhibitor (PI) with potent and pan-genotypic activity. In early studies, it demonstrated a high genetic barrier to resistance with activity against common variants that emerge following exposure to first generation PIs. ABT-530 is an NS5A inhibitor with pan-genotypic activity and a high genetic barrier to resistance, maintaining activity against all common single nucleotide change resistance-associated variants in NS5A in all GTs. ABT-530 is greater than 100-fold more active than the first generation NS5A inhibitors (e.g., daclatasvir and ledipasvir) against key resistance-associated variants. The applicant has co-formulated ABT-493/ABT-530 300 mg/120 mg into a single agent administered together as an oral tablet for 12 weeks. The claim of a fixed-dose combination may have a major impact on the global prevalence and burden of HCV, as it may represent a simple, well-tolerated, highly efficacious pan-genotype treatment for ALL HCV infected subjects. The sponsor is seeking the indication of treatment of adults with chronic genotype 1, 2, 3, 4, 5, or 6 hepatitis C infection with compensated cirrhosis (Child-Pugh classification of severity of cirrhosis).

The combined treatment was an oral film-coated fixed combination formulation, available in these studies as a 300 mg and 120 mg tablet.

The sponsor sponsored four studies in support of this indication: Study Protocol M14-172 for treatment of genotypes 1, 2, 4, 5, and 6 with compensated cirrhosis, Study M15-462 for treatment of all genotypes in renally-impaired-infected subjects, Study M13-590 for treatment of genotype 1 HCV subjects, and Study M13-594 for the treatment of subjects with treatment-naïve GT 3 HCV infection in combination with sofosbuvir and daclatasvir.

**Protocol Study M14-172:** “A single arm, open-label study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis” (EXPEDITION-1)

Subjects: 175 subjects enrolled
Sites: 44 sites worldwide participated

The primary objectives of this study were: 1) to evaluate the effect of response to treatment by evaluating the percentage of subjects achieving a 12-week sustained virologic response
(SVR12) following 12 weeks of treatment with ABT-493/ABT-530 and to evaluate the safety of ABT-493/ABT-530 in adults with cirrhosis HCV GT 1, 2, 4, 5, and 6 infection and compensated cirrhosis, and 2) to assess the percentage of subjects with on-treatment virologic failure or relapse at 12 weeks.

This protocol was an international, phase 3, single arm, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in chronic HCV GT1, 2, 4, 5, or 6-infected subjects with compensated cirrhosis who are either HCV treatment-naïve or prior treatment experienced (i.e., IFN or PegIFN with or without RBV, or SOF plus RBV with or without pegIFN). A target of 175 subjects with documented chronic genotype 1, 2, 4, 5, or 6 HCV infections were randomized. The numbers of subjects infected with each GT were assigned as follows: GT1 had a maximum of 65 subjects enrolled. GT2 had a maximum of 45 subjects enrolled. GT4 had a maximum of 35 subjects enrolled, and 30 subjects with GT 5 and 6 with compensated cirrhosis were enrolled. Subjects were randomized to either treatment groups:

- Treatment Period: Eligible subjects were enrolled to receive ABT-493/ABT-530 300 mg QD for 12 weeks.
- Post Treatment Period: Subjects who completed or permanently discontinued the Treatment Period were followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral variants.

Subjects were randomized by genotypes and the presence or absence of cirrhosis at screening. **Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection or malignancy or transplantation were excluded.**

Protocol Study M15-462: “A single arm, open-label study to evaluate the efficacy and safety of ABT-493/ABT-530 in renally-impaired adults with chronic hepatitis C virus genotype 1-6 infections” (EXPEDITION-4).

Subjects: 100 subjects were enrolled
Sites: 40 sites worldwide participated

The primary objectives of this study were: 1) to evaluate the response to treatment by evaluating the percentage of subjects achieving a 12-week sustained virologic response (SVR12) following 12 weeks of treatment with ABT-493/ABT-530 and to evaluate the safety of ABT-493/ABT-530 in adults with cirrhosis and HCV GT 1 infection with chronic renal impairment, and 2) to assess the percentage of subjects with on-treatment virologic failure or with post- treatment relapse after 12 weeks.
This protocol was an international, phase 3, single arm, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 for 12 weeks in chronic HCV GT 1-6-infected treatment-naïve or treatment experienced (i.e., IFN or PegIFN with or without RBV, PegIFN/RBV plus SOF, or SOF plus RBV) adults with or without compensated cirrhosis who have severe renal impairment ESRD. Fifty (50) subjects with documented chronic GT 1 infection were enrolled. The remaining subjects enrolled were GT2, 3, 4, 5, or 6-infected subjects. Among HCV GT3-infected subjects, only treatment naïve subjects with or without compensated cirrhosis was eligible for enrollment. Treatment-experienced subjects with GT3 were not allowed to enroll. Subjects were randomized to either treatment group:

- Treatment Period: Eligible subjects were enrolled to receive ABT-493/ABT-530 300 mg QD for 12 weeks.
- Post Treatment Period: Subjects who completed or prematurely discontinue the Treatment Period were followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral variants.

Subjects were stratified by the presence or absence of kidney disease at screening and prior treatment experience (treatment naïve vs treatment experienced). Subjects were stratified per genotype. Post treatment HCV RNA results were blinded to the investigator.

**Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection will be excluded.**

**Protocol Study M13-590:** “A randomized, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus genotype 1 infection” (ENDURANCE-1).

Subjects: 620 subjects enrolled
Sites: 130 sites worldwide participated

The primary objectives of this study were: 1) to show the non-inferiority of the SVR 12 rates among mono-infected HCV GT1 DAA-naïve subjects (the percentage of subjects achieving an 12-week sustained virologic response, SVR 12 for 12 weeks of treatment with the combination regimen with ABT-493/ABT-530 to the historical SVR rate established by current approved standard of care regimens for mono-infected HCV GT1 DAA-naïve subjects, and 2) to assess the safety of 8 and 12 weeks of treatment with the combination regimen ABT-493/ABT-530.

This protocol was an international, phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of the ABT-493/ABT-530 combination regimen in HCV-treatment naïve or prior treatment-experienced (i.e., IFN or PegIFN with or without RBV, or SOF plus RBV with or without RBV, or SOF plus RBV with or without pegIFN) chronic HCV GT1-infected of HCV GT1/HIV-1 co-infected subjects without cirrhosis for 8-and 12 weeks.
treatment durations. The study consisted of two periods:

- **Treatment Period**: Eligible subjects were enrolled to receive 8 or 12 weeks of ABT-493/ABT-530.
- **Post Treatment Period**: Subjects who completed or prematurely discontinued the Treatment Period were followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral variants. HCV GT1-infected treatment-naïve or prior treatment experienced subjects without cirrhosis were enrolled into one of two arms (310 subjects per arm):

  - **Arm A**: ABT-493/ABT-530 (300 mg/120 mg QD) for 12 weeks
  - **Arm B**: ABT-493/ABT-530 (300 mg/120 mg QD) for 8 weeks.

Subjects meeting all eligibility criteria were randomized in a 1:1 ratio to Arms A or B. The randomization was stratified by Screening viral load (< or > million IU/mL) and by HCV GT1 subtype (1b or non-1b).

**Subjects with any liver disease of non-HCV etiology or hepatitis B co-infection were excluded.**

**Protocol Study M13-594**: “A randomized, open-label, active-controlled, multicenter study to compare the efficacy and safety of ABT-493/ABT-530 to sofosbuvir co-administered with daclatasvir in adults with chronic hepatitis C virus genotype 3 infections” (ENDURANCE-3).

Subjects: 400 subjects enrolled  
Sites: 70 sites globally participated

The primary objective of this study was to demonstrate non-inferiority in the percentage of subjects achieving a 12-week sustained virologic response, (SVR 12) of 12 weeks of treatment with ABT-493/ABT-530 to 12 weeks of treatment with SOF and DCV, to demonstrate non-inferiority of 8 weeks of treatment with ABT-403/ABT-503, and to assess the safety of ABT-493/ABT-530 compared to SOF and DCV in adults with chronic HCV GT3 infection.

This protocol was an international, phase 3, randomized, open-label, active-controlled multicenter study to compare efficacy and safety of ABT-493/ABT-530 to SOF and DCV in treatment-naïve chronic HCV GT3-infected subjects without cirrhosis.

The study consisted of two periods:

- **Treatment Period**: Eligible subjects were enrolled to receive 12 or 8 weeks of ABT-493/ABT-530 or 12 weeks of SOF with DCV
- **Post-Treatment Period**: Subjects who completed or prematurely discontinued the Treatment Period were followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of
viral variants HCV GT3-infected treatment-naïve subjects without cirrhosis were enrolled into one of three arms:

Arm A: ABT-493/ABT-530 (300 mg/120 mg QD) for 12 weeks
Arm B: SOF 400 mg + DCV 60 mg QD for 12 weeks
Arm C: ABT-493/ABT-530 (300 mg/120mg QD for 8 weeks)

Subjects meeting all eligibility criteria were randomized in a 2:1 ratio to Arms A or B with 230 subjects randomized to Arm A and 115 subjects randomized to Arm B. After enrollment to Arms A and B was completed, 115 subjects were assigned to Arm C.

The CDER review division team and OSI with input from statistics were involved in the selection process. The sites were selected principally due to relatively high patient accrual in the study and site specific protocol violations. The clinical site inspections were intended to verify the data integrity. Five domestic site inspections covering three protocols and three foreign site inspections inspecting two protocols were requested for this submission. Two sites were identified per pivotal trial to include all forms of genotypes G1-6. According to the consult, specific reasons for site selection include a relatively large number of protocol deviations and variability in adverse events reporting among other sites. Justification for foreign site inspections were 1) that this is the first approval of this new fixed drug combination/formulation, 2) verification of the quality of conduct of Study M14-562, and 3) because HCV Genotype 3 is more prevalent in foreign countries than US.

Number of subjects: 802 randomized; (533 1200 mg QD: 269 400mg BID)
Number of sites: 151; of the 151 sites, 139 allocated subjects
Participant countries: Globally, 31 centers in the U.S.
Trial initiation date: May 26, 2014
Trial completion date: December 2, 2015
Study report date: May 12, 2016

Site Selection for Study Protocols

Site #53216 in Greece (Dr. Papatheodoridis) had a relatively high enrollment and low adverse events. Site #47437 in Belgium (Dr. Bourgeois) had the highest adverse events and protocol violations. Site #58429 in France (Dr. Leroy) had high enrollment. None of the foreign sites had a history of previous inspection in our FDA database. Site #18161 in California (Dr. Felizarta) had relatively high enrollment and low adverse events compared to other sites. This site had very high number of INDs and three previous inspections; 2 NAIs and one VAI. Site #37759 in Texas (Dr. Ghalib) had the highest enrollment and highest adverse events among other sites. This site had one prior inspection classified as NAI. Site #12641 in California (Dr. Lalezari) had the highest U.S. enrollment and two previous CDER inspections both NAIs. Site #81470 (Dr. Zogg) had high enrollment, higher adverse events and protocol deviations,
and no prior history of inspection. Site #59308 in Portland (Dr. Jazrawi) had a relatively high enrollment in the U.S., and no prior history of inspection.

### III. RESULTS (by site):

<table>
<thead>
<tr>
<th>Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.</th>
<th>Protocol # and # of Subjects</th>
<th>Inspection Date</th>
<th>Final Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgios Papatheodoridis, M.D. 17agion Thoma, Attiki Greece,11527 Site #53216</td>
<td>M 15-462 Subject=Enrolled 8</td>
<td>3/13-16/2017</td>
<td>Pending (preliminary classification NAI)</td>
</tr>
<tr>
<td>Vincent Leroy, M.D. Grenobl Cedex CEDEX 9 Rhone –Aloes France 38043 Site #58420</td>
<td>M15-462 Subjects=Enrolled 9</td>
<td>4/3-6/2017</td>
<td>Pending (preliminary classification NAI)</td>
</tr>
<tr>
<td>Franco Felizarta M.D. 3535 San Dimas St. Suite 24 Bakersfield, CA 93301 Site #18161</td>
<td>M14-172 Subjects=Enrolled 8</td>
<td>3/1-3 &amp; 3/6/2017</td>
<td>Pending (preliminary classification NAI)</td>
</tr>
<tr>
<td>Jacob Lalezari, M.D. 2300 Sutter St. San Francisco, CA 94115 Site#12641</td>
<td>M14-172 Subjects= 12 Enrolled</td>
<td></td>
<td>Pending (preliminary classification NAI)</td>
</tr>
<tr>
<td>Stefan Bourgeois, M.D. Lange Beeldakensstraat 267 Antwerp 2060 Belgium Site# 47437</td>
<td>M13-590 Subjects= 12 Enrolled</td>
<td></td>
<td>Pending (preliminary classification NAI)</td>
</tr>
<tr>
<td>Saad Jazrawi, M.D. 1130 Northwest 22nd Avenue Portland OR 97210 Site# 59308</td>
<td>M13-594 Subjects = 11 Enrolled</td>
<td>3/14-23/2017</td>
<td>VAI</td>
</tr>
</tbody>
</table>
Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on 100% review of informed consent documents, IRB, ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. Georgios Patheodoridis, M.D./Site #53216/Study M15-462
   Attiki, Greece 11527

   There were 8 subjects screened, eight subjects were enrolled in the study, and one subject discontinued due to adverse event. Seven subjects completed the study.
   The medical records for all subjects were reviewed for informed consent and primary efficacy endpoints. Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting. In few subjects minor protocol deviations were found regarding visits out-of-window, ECGs for screening were done after blood collection instead of prior per protocol. The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr. Papatheodoridis.

   With the exceptions of the minor deviations noted above, the data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the acceptability of the data submitted in support of the application.

2. Vicenct Leroy, M.D./Site #58420/Study M15-462
   Rhone-Aloes, France 38043

   There were 9 subjects screened, nine subjects enrolled, and all nine subjects
completed the study. The field investigator reported that the primary endpoints were verified at the site. Two subjects (404602 and 404608) experienced adverse events during the follow-up phase of the study. Subject #404602 experienced chest pain, and Subject #404608 had dilation in both legs. These adverse events were reported to the sponsor and IRB and were not drug related.

The medical records for all subjects were reviewed. Records were organized and legible. Medical records/source documents were compared to data listings for primary efficacy endpoint and adverse events reporting. No major deficiencies were observed. The audit revealed adequate adherence to the regulations and investigational plan.

At the conclusion of the inspection, no Form 483 was issued to Dr. Leroy. The field investigator noted minor protocol deviations regarding ECG for one subject not taken at Visit 8, and the missing alpha feroprotein results for another subject. It is unlikely that the protocol deviations would have impacted the outcome of the study in terms of validity or reliability of the submitted data. No data integrity issues were found and no safety concerns were noted.

With the exceptions noted above, the data generated at Dr. Leroy’s site for M15-462 in support of clinical efficacy and safety is considered reliable and may be used in support of the pending application.

3. Reem Ghalib, M.D./ Site #37759/Study M14-172
Arlington, TX 76012

There were 21 subjects screened, 11 subjects were reported as screen failures, and 10 subjects were enrolled. All 10 subjects completed the study. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted, however, Subject #612516 experienced an adverse event that was reported to the sponsor and IRB because the subject took aspirin and had a GI bleed. The clinical investigator considered the event not drug related to the study drug. The review division was informed that the sponsor should be reporting the adverse event to the FDA. The medical officer stated that she will check to see if the adverse event was later reported. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. The field investigator reported that the medical records were organized and legible.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.
4. **Franco Felizarta, M.D./ Site #18161/Study M14-172**
   Bakersfield, CA 93301

   There were 12 subjects screened, four subjects were reported as screen failures, eight subjects were randomized, and 8 subjects completed the study. The medical records/source documents for all enrolled subjects were reviewed.

   The medical records/source documents were compared to case report forms and data listings and they were consistent. No under-reporting of adverse events was found. The primary efficacy endpoint was verifiable. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspective Observations but issued.

   The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

5. **Jacob Lalezari, M.D./ Site #12641/Study M13-590**
   San Francisco, CA 94115

   There were 19 subjects screened, seven subjects were reported as screen failures, and 12 subjects were enrolled. There was one subject reported as lost-to-follow up at Week 24, but the subject completed the study. All enrolled subjects completed the study. The medical records for all subjects were reviewed.

   The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. At the conclusion of the inspection, no FDA 483 was issued to the clinical investigator. However, the ORA investigator noted and discussed with the clinical investigator few items regarding the write-overs and the out-of-window visits. The clinical investigator and the staff acknowledged the findings.

   No data integrity issues were found and no safety concerns were noted. The data generated at Dr. Lalezari’s site in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

6. **Stefan Bourgeois, M.D./ Site #47437/Study M13-590**
   2060 Antwerp, Belgium

   There were 14 subjects screened, five subjects were reported as screen failures, and nine subjects were enrolled. All enrolled subjects completed the study. The medical records for all subjects were reviewed.

   The medical records/source documents for nine subjects were compared to case report form
and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were observed. At the conclusion of the inspection, no FDA 483 was issued to the clinical investigator. No data integrity issues were found and no safety concerns were noted.

The data generated at Dr. Bourgeois’s site in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

7. Saad Jazrawi, M.D./ Site #59308/Study M13-594
Portland, OR 972110

There were 18 subjects screened, one subject was rescreened, seven subjects were reported as screen failures, and 11 subjects were enrolled. All enrolled subjects completed the study. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. At the conclusion of the inspection, a 1-item FDA 483 was issued to the clinical investigator. The field investigator noted inadequate documentation to confirm that Subject #156316 met inclusion criteria regarding HCV RNA results or ALT levels to show that the subject met inclusion criteria at least 6 months prior to screening as specified by the protocol.

The clinical investigator agreed with the observation in a written response dated 3/27/2017, in which he implemented corrective action plan to remedy the situation. OSI finds his response acceptable. It is unlikely that the deviation impacts the outcome of the study in terms of validity or reliability of the submitted data. No data integrity issues were found and no safety concerns were noted.

With the exceptions noted above, the data generated at Dr. Jazrawi’s site in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

8. Donald Zogg, M.D./ Site #81470/Study M13-594
St. Paul, MN 55114

There were 13 subjects screened, four subjects were reported as screen failures, and 9 subjects were enrolled. Subject 167303 chose to stop study medication early after becoming pregnant (“missed abortion”) which was reported as a serious adverse event “The clinical investigator considered the event of missed abortion as having no reasonable possibility of being related to study drug and more likely related to risk factors of prior miscarriage and elective abortion”. However, the subject continued her visits and was considered to have completed the study. All enrolled subjects completed the study. The medical records for all subjects were reviewed. No data integrity issues were found and no
safety concerns were noted.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. Minor deficiencies were observed. At the conclusion of the inspection, a 1-item FDA 483 was issued to the clinical investigator regarding the lack of documentation to show the investigational product kit numbers dispensed and returned. The clinical investigator stated the kit numbers that were assigned to the study subjects were provided by the sponsor through the Interactive Response Technology (IRT) system. The clinical investigator provided a written response dated 3/10/2017 in which he agreed with observation and instituted a corrective action plan to remedy the situation. OSI finds his response to be acceptable.

With the exception of the above noted observation, the data generated at Dr. Zogg’s site in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

CONCURRENCE:

See appended electronic signature page

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

See appended electronic signature page

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

Reference ID: 4090590
CC:

Central Doc. Rm. NDA 209394
DAVP /Division Director/Debra Birnkrant
DAVP /Medical Team Leader/Wendy Carter
DAVP /Project Manager/Alicia Moruf
DAVP/Medical Officer/Lara Stabinski
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCPAB/Reviewer/Antoine El Hage
OSI/DCCE/GCP Program Analysts/Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTOINE N EL HAGE
04/28/2017

SUSAN D THOMPSON
04/28/2017

KASSA AYALEW
04/28/2017

Reference ID: 4090590
REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209394

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Glecaprevir/Pibrentasvir (GLE/PIB) co-formulated film-coated bilayer tablets

Applicant: AbbVie Inc.

Receipt Date: December 14, 2016

Goal Date: August 14, 2017

1. Regulatory History and Applicant’s Main Proposals

On October 15, 2012, AbbVie Inc. submitted IND 116169 and IND 116170, ABT-493 and ABT-530 respectively and on October 16, 2015 submitted IND 127416 for the fixed dose combination tablet of ABT-493 and ABT-530. Glecaprevir (ABT-493, GLE), is a hepatitis C virus (HCV) nonstructural (NS) 3/4A protease inhibitor (PI), and pibrentasvir (ABT-530, PIB) is an NS5A inhibitor.

This direct-acting antiviral agent (DAA) combination regimen is currently being evaluated in eight registrational studies for the treatment of chronic HCV genotypes (GTs) 1 to 6 infection. Studies M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, M15-410 Part 2, M14-868 Part 3, and M14-868 Part 4 will be used in support of a once daily (QD), ribavirin (RBV)-free oral dose across all genotypes in subjects with compensated liver disease with and without cirrhosis including HCV/human immunodeficiency virus (HIV) co-infected, subjects treatment-experienced to previous PI and/or NS5A inhibitors (TE-PI/NS5A), and subjects with chronic kidney disease (CKD) Stages 4 and 5, using treatment durations for 8 to 12 weeks, with an option for 16 weeks for more difficult to treat populations.

2. Review of the Prescribing Information

This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements of Prescribing Information (SRPI)” checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information
The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

**Highlights**

See Appendix for a sample tool illustrating Highlights format.

**HIGHLIGHTS GENERAL FORMAT**

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

*Comment:*

**YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.

*Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.*

*Comment: Applicant submitted waiver request for length of HL due to expected addition of boxed warning language*

**YES** 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), and
- TOC from the Full Prescribing Information (FPI).

*Comment:*

**YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPERCASE letters. See Appendix for HL format.

*Comment:*

**YES** 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 for HL format.

*Comment:*

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

*Comment:*

**YES** 7. Heads in HL must be presented in the following order:

<table>
<thead>
<tr>
<th>Heading</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>• Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>• Initial U.S. Approval</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

- Boxed Warning: Required if a BOXED WARNING is in the FPI
- Recent Major Changes: Required for only certain changes to PI* 
- Indications and Usage: Required 
- Dosage and Administration: Required 
- Dosage Forms and Strengths: Required 
- Contraindications: Required (if no contraindications must state “None.”) 
- Warnings and Precautions: Not required by regulation, but should be present 
- Adverse Reactions: Required 
- Drug Interactions: Optional 
- Use in Specific Populations: Optional 
- Patient Counseling Information Statement: Required 
- Revision Date: Required

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

YES 10. Product title must be bolded. 

Comment: The trade name is not yet bolded as its under review

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be bolded, and include the verbatim statement “Initial U.S. Approval;” followed by the 4-digit year.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be bolded.

Comment: Placeholder for expected Boxed Warning but does not contain language as of yet

YES 13. The BW must have a title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. Even if there is more than one warning, the term “WARNING” and not “WARNINGS” should be used. For example: “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the
Selected Requirements of Prescribing Information

BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:** Placeholder for expected Boxed Warning but does not contain language as of yet

**YES 14.** The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement must be placed immediately beneath the BW title, and should be centered and appear in italics.

**Comment:** Placeholder for expected Boxed Warning but does not contain language as of yet

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

**Comment:** placeholder for expected Boxed Warning but does not contain language as of yet

Recent Major Changes (RMC) in Highlights

**N/A 16.** RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015.”

**Comment:**

**N/A 18.** A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

Dosage Forms and Strengths in Highlights

**N/A 19.** For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:** One dosage form only

Contraindications in Highlights

**YES 20.** All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

**Comment:**

Adverse Reactions in Highlights
Selected Requirements of Prescribing Information

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

*Comment:*

Patient Counseling Information Statement in Highlights

YES 22. 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 (or will have)** FDA-approved patient labeling:

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

*Comment:*

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 8/2015”).

*Comment:*
Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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:

YES 26. The same title 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 27. In the TOC, all section headings must be bolded and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:
FULL PRESCRIBING INFORMATION: GENERAL FORMAT

31. 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.

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

**Comment:**

32. 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)].”

**Comment:**

Reference ID: 4048993
33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading “FULL PRESCRIBING INFORMATION” must be bolded, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be bolded.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “WARNING” and not “WARNINGS” should be used.) For example: “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“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 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:
PATIENT COUNSELING INFORMATION Section in the FPI

40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

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

Comment:
Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

8.2
8.3
8.4
8.5
8.6
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICIA MORUF
01/31/2017
**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)]

<table>
<thead>
<tr>
<th>Application Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDA #</strong> 209394</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Proprietary Name: under review  
Established/Proper Name: Glecaprevir/Pibrentasvir (GLE/PIB)  
Dosage Form: tablets  
Strengths: 100 mg glecaprevir and 40 mg pibrentasvir  
Route(s) of Administration: oral  
Applicant: AbbVie  
Agent for Applicant (if applicable):  
Date of Application: 12/14/2016  
Date of Receipt: 12/14/2016  
Date clock started after Unacceptable for Filing (UN): N/A  
PDUFA/BsUFA Goal Date: 08/14/2017  
Action Goal Date (if different): N/A  
Filing Date: 02/12/2017  
Date of Filing Meeting: 01/13/2017  

Chemical Classification (original NDAs only):  
☑ Type 1- New Molecular Entity (NME); NME and New Combination  
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination  
☐ Type 3- New Dosage Form; New Dosage Form and New Combination  
☐ Type 4- New Combination  
☐ Type 5- New Formulation or New Manufacturer  
☐ Type 7- Drug Already Marketed without Approved NDA  
☐ Type 8- Partial Rx to OTC Switch  
☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)  
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)  

Proposed indication(s)/Proposed change(s): For the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection  

Type of Original NDA:  
☐ AND (if applicable)  
☐ Type of NDA Supplement:  
☑ 505(b)(1)  
☐ 505(b)(2)  
If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:  

Type of BLA  
☐ 351(a)  
☐ 351(k)

Reference ID: 4044163
Review Classification:

*The application will be a priority review if:*

- A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)
- The product is a Qualified Infectious Disease Product (QIDP)
- A Tropical Disease Priority Review Voucher was submitted
- A Pediatric Rare Disease Priority Review Voucher was submitted

<table>
<thead>
<tr>
<th>Resubmission after withdrawal?</th>
<th>N/A</th>
<th>Resubmission after refuse to file?</th>
<th>N/A</th>
</tr>
</thead>
</table>

**Part 3 Combination Product? N/A**

*If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults*

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

- Fast Track Designation via IND 116169
- Breakthrough Therapy Designation via IND 127416 (set the submission property in DARTTS and notify the CDER Breakthrough Therapy Program Manager)
- Rolling Review
- Orphan Designation
- Rx-to-OTC switch, Full
- Rx-to-OTC switch, Partial
- Direct-to-OTC

**Other: N/A**

**Collaborative Review Division (if OTC product): N/A**

**List referenced IND Number(s):** IND 127416, IND 116169, IND 116170

### Goal Dates/Product Names/Classification Properties

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDUFA/BsUFA and Action Goal dates correct in the electronic archive?</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.*

| Are the established/proper and applicant names correct in electronic archive? | ☑  |    |    |         |

*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 electronic archive.*
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:  

If no, ask the document room staff to make the appropriate entries.

<table>
<thead>
<tr>
<th>Application Integrity Policy</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)? 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></td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, explain in comment column.</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

If affected by AIP, has OC been notified of the submission?  
If yes, date notified:  

<table>
<thead>
<tr>
<th>User Fees</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

User Fee Status

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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.

Payment for this application (check daily email from UserFeeAR@fda.hhs.gov):

- ☒ Paid
- ☐ Exempt (orphan, government)
- ☐ Waived (e.g., small business, public health)
- ☐ Not required

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. Contact the User Fee Staff. If appropriate, send UN letter.

Payment of other user fees:

- ☐ Not in arrears
- ☒ In arrears

User Fee Bundling Policy

Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:  

Has the user fee bundling policy been appropriately applied? If no, or you are not sure, consult the User Fee Staff:

- ☒ Yes
- ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)

<table>
<thead>
<tr>
<th>505(b)(2) (NDAs/NDA Efficacy Supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</td>
<td>☐</td>
<td>☒</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
- 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)].

- 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)]?

If you answered yes to any of the above bulleted 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 for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<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>
</tbody>
</table>

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.
<table>
<thead>
<tr>
<th>Exclusivity</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does another product (same active moiety) have orphan exclusivity for the same indication? <strong>Check the Orphan Drug Designations and Approvals list at:</strong> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If yes, # years requested: 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, contact the Orange Book Staff (CDER-Orange Book Staff)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Format and Content

*Do not check mixed submission if the only electronic component is the content of labeling (COL).*

- All paper (except for COL)
- All electronic
- Mixed (paper/electronic)
- CTD
- Non-CTD
- Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If electronic submission, does it follow the eCTD guidance?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If not, explain (e.g., waiver granted).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index:</strong> Does the submission contain an accurate comprehensive index?</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ legible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☒ English (or translated into English)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ pagination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☒ navigable hyperlinks (electronic submissions only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, explain.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLAs only:</strong> Companion application received if a shared or divided manufacturing arrangement?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If yes, BLA #</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Forms and Certifications

*Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.*

**Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

<table>
<thead>
<tr>
<th>Application Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---


Version: 12/05/2016
| **Patent Information**  
(NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Financial Disclosure</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*

*Note:* Financial disclosure is required for bioequivalence studies that are the basis for approval.

<table>
<thead>
<tr>
<th><strong>Clinical Trials Database</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”*

*If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant*

<table>
<thead>
<tr>
<th><strong>Debarment Certification</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Certification is not required for supplements if submitted in the original application. If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*

*Note:* Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge…”

| **Field Copy Certification**  
(NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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)*

*If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*
<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td>☒</td>
<td></td>
<td></td>
<td>Based upon an evaluation of these data, there appears to be no potential for abuse of these compounds and, therefore, AbbVie recommends that no further studies be performed to address abuse potential. In addition, AbbVie recommends that glecaprevir/pibrentasvir not be added to any schedule by the Controlled Substances Act</td>
</tr>
<tr>
<td>For non-NMEs: Date of consult sent to Controlled Substance Staff:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREA</td>
<td></td>
<td></td>
<td></td>
<td>Scheduled for PeRC on July 12, 2017</td>
</tr>
<tr>
<td>Does the application trigger PREA?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</td>
<td>☒</td>
<td></td>
<td></td>
<td>IND 127416 submission dated 06/16/2016 EDR Link: \CDSESUB1\evsprod\IND127416\0043</td>
</tr>
<tr>
<td>If no, may be an RTF issue - contact DPMH for advice.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</td>
<td></td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, may be an RTF issue - contact DPMH for advice.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPCA: Is this submission a complete response to a pediatric Written Request?</td>
<td></td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm)

3. [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm)
<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a proposed proprietary name submitted?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REMS</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a REMS submitted?</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescription Labeling</th>
<th>Not applicable</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Check all types of labeling submitted.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Is Electronic Content of Labeling (COL) submitted in SPL format? | ☒ | ☐ | ☐ | |
| If no, request applicant to submit SPL before the filing date. | | | | |

| Is the PI submitted in Physician Labeling Rule (PLR) format? | ☒ | ☐ | ☐ | |
| If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? | | | | |
| If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date. | | | | |

| For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (format? PLLR) | ☒ | ☐ | ☐ | |
| Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included? | ☒ | ☐ | ☐ | |
| PI does not contain section 8.3 | | | | |
| Located in the common technical documents folder under toxicology summary | | | | |

| For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? | ☐ | ☐ | ☒ | |
| If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date. | | | | |

---


Version: 12/05/2016

Reference ID: 4044163
Has all labeling ([PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling]) been consulted to OPDP?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? *(send WORD version if available)*

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OTC Labeling**

<table>
<thead>
<tr>
<th></th>
<th>Not Applicable</th>
</tr>
</thead>
</table>

Check all types of labeling submitted.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is electronic content of labeling (COL) submitted?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If no, request in 74-day letter.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are annotated specifications submitted for all stock keeping units (SKUs)?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If no, request in 74-day letter.

Are representative labeling is submitted, are all represented SKUs defined?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If no, request in 74-day letter.

All labeling/packaging sent to OSE/DMEPA?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other Consults**

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, specify consult(s) and date(s) sent:

**Meeting Minutes/SPAs**

End-of Phase 2 meeting(s)?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date(s):</td>
<td>cancelled per request of applicant, see 11/16/2016 preliminary comments which serve as the official meeting minutes of the EOP2 meeting under IND 116169 and 116170.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?

| Date(s): | November 3, 2016 Type B pre-NDA |

Any Special Protocol Assessments (SPAs)?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Version: 12/05/2016
DATE: 01/12/2017

BACKGROUND:

On October 15, 2012, AbbVie Inc. submitted IND 116169 and IND 116170, ABT-493 and ABT-530 respectively and on October 16, 2015 IND 127416 was submitted for the fixed dose combination tablet of ABT-493 and ABT-530. Glecaprevir (ABT-493, GLE), is a hepatitis C virus (HCV) nonstructural (NS) 3/4A protease inhibitor (PI), and pibrentasvir (ABT-530, PIB) is an NS5A inhibitor. This direct-acting antiviral agent (DAA) combination regimen is currently being evaluated in eight registrational studies for the treatment of chronic HCV genotypes (GTs) 1 to 6 infection. Studies M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, M15-410 Part 2, M14-868 Part 3, and M14-868 Part 4 will be used in support of a once daily (QD), ribavirin (RBV)-free oral dose across all genotypes in subjects with compensated liver disease with and without cirrhosis including HCV/human immunodeficiency virus (HIV) co-infected, subjects treatment-experienced to previous PI and/or NS5A inhibitors (TE-PI/NS5A), and subjects with chronic kidney disease (CKD) Stages 4 and 5, using treatment durations for 8 to 12 weeks, with an option for 16 weeks for more difficult to treat populations.

Reference is made to the May 26, 2016 Type C Written Responses Only communication in which agreement was reached between the Agency and AbbVie Inc. on the adequacy of the nonclinical data package, the Statistical Analysis Plan (SAP) for the Integrated Summaries efficacy and Safety (ISE and ISS), and the Integrated Resistance Analysis Plan (IRAP) in preparation for the NDA submission later this year.

AbbVie Inc. requested a Type B, pre-NDA meeting on August 4, 2016 to obtain Agency agreement on the adequacy of the clinical package for the planned NDA submission in December 2016. A face to face meeting was granted for November 3, 2016. AbbVie provided a meeting package on October 7, 2016.

On November 3, 2016 Type B pre-NDA meeting where the Division of Antiviral Products (DAVP) agreed that the clinical data were sufficient to support submission of the NDA and that the planned content of the NDA appeared adequate. DAVP also agreed that the Expert Hepatic Panel assessment could be submitted during the NDA review. Per subsequent agreement dated December 13, 2016, the assessment for the prioritized 10 subjects (7 subjects with total bilirubin $\geq 2 \times$ ULN with direct/mixed predominance and other hepatic events of interest) will be submitted by January 31, 2017. The EHP assessment for the additional 23 subjects who had total bilirubin $\geq 2 \times$ ULN with indirect predominance will be submitted as expeditiously as possible, but likely after January 31, 2017.

On December 14, 2016 AbbVie Inc., submitted an NME NDA 209394 for review.
## REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Alicia Moruf</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Elizabeth Thompson</td>
<td>Y</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Jeff Murray</td>
<td>N</td>
</tr>
<tr>
<td>Division Director/Deputy</td>
<td>Deb Birnkrant</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Jeff Murray</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Adam Sherwat, acting for Director today</td>
<td>Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>Ed Cox</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>John Farley</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Larissa Stabinski</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Wendy Carter</td>
<td>Y</td>
</tr>
<tr>
<td>Social Scientist Review (for OTC products)</td>
<td>Reviewer: N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TL: N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>OTC Labeling Review (for OTC products)</td>
<td>Reviewer: N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TL: N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical Microbiology (for antimicrobial products)</td>
<td>Reviewer: P. Harrington E.Donaldson</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: J. O’Rear</td>
<td>N</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Ayyoub, Amal</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Islam Younis</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Mario Sampson Acting</td>
<td>Y</td>
</tr>
<tr>
<td>Genomics</td>
<td>Reviewer: Simbarashe Zvada</td>
<td>Y</td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>TL: Jeff Florian</td>
<td>N</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Reviewer: Therri Usher</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>LaRee Tracy</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Thamban Valappil</td>
<td>Y</td>
</tr>
<tr>
<td>Section</td>
<td>Reviewer</td>
<td>TL:</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Ilona Bebenek</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Hanan Ghantous</td>
<td>N</td>
</tr>
<tr>
<td>Statistics (carcinogenicity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Quality (CMC) Review Team:</td>
<td>ATL: Stever Miller</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>RBPM: Luz Rivera</td>
<td>N</td>
</tr>
<tr>
<td>• Drug Substance</td>
<td>Raymond Frankewich</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Kasturi Srinivasachar</td>
<td>Secondary</td>
</tr>
<tr>
<td>• Drug Product</td>
<td>Danuta Gromek-Woods</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>(Primary) Shanmugam,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balajee – (Secondary)</td>
<td></td>
</tr>
<tr>
<td>• Process</td>
<td>Ying Wang (Primary)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Upinder Atwal (Secondary)</td>
<td></td>
</tr>
<tr>
<td>• Microbiology</td>
<td>Ying Wang (Primary)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Upinder Atwal (Secondary)</td>
<td></td>
</tr>
<tr>
<td>• Facility</td>
<td>Christina Capacci –Daniel</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>(Primary) Derek Smith</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((Secondary)</td>
<td></td>
</tr>
<tr>
<td>• Biopharmaceutics</td>
<td>Gerlie Gieser</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Elsbeth Chikhale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>• Immunogenicity</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Labeling (BLAs only)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Other (e.g., Branch Chiefs, EA Reviewer)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>OMP/OMPI/DMPP (MedGuide, PPI, IFU)</td>
<td>Sharon Mills</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Barbara Fuller</td>
<td>N</td>
</tr>
<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)</td>
<td>Wendy Lubarsky</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OSE/DEPI</td>
<td>Mingfeng Zhang</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Natasha Pratt</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name, carton/container labeling)</td>
<td>Valerie Wilson;</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Vicky Borders-Hemphill</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td>Elizabeth Everhart</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Naomi Redd</td>
<td>N</td>
</tr>
<tr>
<td>OC/OSI/DSC/PMSB (REMS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FILING MEETING DISCUSSION:

GENERAL

• 505(b)(2) filing issues:
  o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
  o Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?

  Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):

  □ Not Applicable  □ YES  □ NO  □ YES  □ NO

• Per reviewers, are all parts in English or English translation?

  If no, explain:

  □ Not Applicable  □ YES

• Electronic Submission comments

  List comments:

  □ Not Applicable  □ No comments
**CLINICAL**

**Comments:**

- Clinical study site(s) inspections(s) needed?
  - If no, explain:

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
</tr>
</tbody>
</table>

- Advisory Committee Meeting needed?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
</tr>
</tbody>
</table>

  **Comments:**

  *If no, for an NME NDA or original BLA, include the reason. For example:*
  - this drug/biologic is not the first in its class
  - the clinical study design was acceptable
  - the application did not raise significant safety or efficacy issues
  - 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

- 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?

<table>
<thead>
<tr>
<th>Not Applicable</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

  **Comments:**

  **CONTROLLED SUBSTANCE STAFF**

- Abuse Liability/Potential

<table>
<thead>
<tr>
<th>Not Applicable</th>
<th>FILE</th>
<th>REFUSE TO FILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Reference ID: 4044163
<table>
<thead>
<tr>
<th>Comments:</th>
<th>□ Review issues for 74-day letter</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL MICROBIOLOGY</td>
<td>□ Not Applicable</td>
</tr>
<tr>
<td></td>
<td>□ FILE</td>
</tr>
<tr>
<td></td>
<td>☑ REFUSE TO FILE</td>
</tr>
<tr>
<td>Comments:</td>
<td>□ Review issues for 74-day letter</td>
</tr>
</tbody>
</table>
CLINICAL PHARMACOLOGY

Comments:
- Clinical pharmacology study site(s) inspections(s) needed?
  - YES
  - NO

BIOSTATISTICS

Comments:

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)

Comments:

PRODUCT QUALITY (CMC)

Comments:

New Molecular Entity (NDAs only)
- Is the product an NME?
  - YES
  - NO

Environmental Assessment
- Categorical exclusion for environmental assessment (EA) requested?
  - YES
  - NO
  - If no, was a complete EA submitted?
    - YES
    - NO

Facility Inspection
- Establishment(s) ready for inspection?
  - YES
  - NO

Comments:
| Facility/Microbiology Review (BLAs only) | ☒ Not Applicable  
☐ FILE  
☐ REFUSE TO FILE  
☐ Review issues for 74-day letter |
| Comments: |

| CMC Labeling Review (BLAs only) | ☐ Review issues for 74-day letter |
| Comments: |

| APPLICATIONS IN THE PROGRAM (PDUFA V)  
(NME NDAs/Original BLAs) | ☐ N/A  
☒ YES  
☐ NO |
| Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? |
| If so, were the late submission components all submitted within 30 days? |

| ☒ YES  
☐ NO  

We had a general agreement to accept the EHP Assessment after NDA submission we are currently awaiting a timeline for this submission which was agreed upon at the Nov 3, 2016 pre-NDA meeting. |

| ☒ YES  
☐ NO  

What late submission components, if any, arrived after 30 days? |

| ☐ YES  
☒ NO  

None as of yet have arrived. Division agreed that the EHP assessment could be submitted at a time both applicant and Division agreed on. |

| ☒ YES  
☐ NO  

Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? |

| ☒ YES  
☐ NO  

Is a comprehensive and readily located list of all clinical sites included or referenced in the application? |

| ☒ YES  
☐ NO  

Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? |
**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Ed. Cox

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): 03/14/2017

**21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

### REGULATORY CONCLUSIONS/DEFICIENCIES

<table>
<thead>
<tr>
<th>N/A</th>
<th>The application is unsuitable for filing. Explain why:</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
<td>The application, on its face, appears to be suitable for filing.</td>
</tr>
</tbody>
</table>

**Review Issues:**

- ☑ No review issues have been identified for the 74-day letter.
- ☐ Review issues have been identified for the 74-day letter.

**Review Classification:**

- ☐ Standard Review
- ☑ Priority Review

### ACTION ITEMS

- ☑ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).

<table>
<thead>
<tr>
<th>N/A</th>
<th>If RTF, notify everyone who already received a consult request, OSE PM, and RBPM</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>N/A</th>
<th>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.</th>
</tr>
</thead>
</table>

- ☑ If priority review, notify applicant in writing by day 60 (see CST for choices) **Due Friday February 10th, 2017**

- ☑ Send review issues/no review issues by day 74 **Due Friday February 24, 2017**

- ☑ Conduct a PLR format labeling review and include labeling issues in the 74-day letter

- ☑ Update the PDUFA V DARRTS page (for applications in the Program)

<table>
<thead>
<tr>
<th>N/A</th>
<th>Other</th>
</tr>
</thead>
</table>

Annual review of template by OND ADRAs completed: April 2016
<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filing/Planning Meeting</td>
<td>January 13, 2017</td>
<td>11:30AM to 1:00PM</td>
</tr>
<tr>
<td>GAM #1</td>
<td>February 15, 2017</td>
<td>1:00PM to 2:30 PM</td>
</tr>
<tr>
<td>MidCycle Meeting</td>
<td>March 14, 2017</td>
<td>03:00PM to 4:30PM</td>
</tr>
<tr>
<td>Midcycle communication with sponsor</td>
<td>March 15, 2017</td>
<td>1:00PM to 2:00PM</td>
</tr>
<tr>
<td>GAM#2</td>
<td>April 3, 2017</td>
<td>10:30am to 12:00pm</td>
</tr>
<tr>
<td>GAM#3/Labeling</td>
<td>May 2, 2017</td>
<td>10:00AM to 11:30AM</td>
</tr>
<tr>
<td>Pre late cycle internal meeting</td>
<td>May 22, 2017</td>
<td>09:00AM to 10:30AM</td>
</tr>
<tr>
<td>Labeling</td>
<td>June 5, 2017</td>
<td>10:00AM to 11:30AM</td>
</tr>
<tr>
<td>Potential Late Cycle -<strong>confirm</strong></td>
<td>June 14, 2017</td>
<td>01:00PM to 2:30PM</td>
</tr>
<tr>
<td>Labeling</td>
<td>June 27, 2017</td>
<td>09:30am to 11:00AM</td>
</tr>
<tr>
<td>Wrap Up</td>
<td>July 13, 2017</td>
<td>1030AM to 12PM</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICIA MORUF
01/19/2017

Reference ID: 4044163