

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208624Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

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

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NDA/BLA # 208624  
Product Name: VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir)

PMR/PMC Description: Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir (VIEKIRA XR™) in pediatric patients greater than 3 years of age with chronic hepatitis C virus infection, who weigh at least 42 kg and are able to swallow tablets.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/31/2015(submitted)</u>
	Study Completion:	<u>04/30/2022</u>
	Final Report Submission:	<u>08/31/2022</u>
	Other: <u>N/A</u>	<u>N/A</u>

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

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

Adult studies are completed and ready for approval. The review team met with the Pediatric Review Committee (PeRC) on June 8, 2016 and again on July 7, 2016. The second meeting with PeRC was to refine the PREA PMR to have weight based criteria replace the pediatric age criteria which the Division had previously proposed. During the July 7, 2016 meeting, PeRC agreed with the Division to grant deferral for pediatric patients with chronic hepatitis C virus infection, who are greater than 3 years of age and weigh at least 42 kg and are able to swallow the VIEKIRA XR tablets, 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.”

The study is a deferred pediatric trial under PREA to evaluate the safety and treatment response (using virologic response) of ombitasvir, paritaprevir, ritonavir, dasabuvir (VIEKIRA XR) in pediatric patients with chronic hepatitis C virus infection, who are greater than 3 years of age and who weigh at least 42 kg and are able to swallow tablets. The sponsor has an ongoing pediatric (b) (4) under the approved NDA for VIEKIRA PAK (NDA 206619) (b) (4)

As such, the milestone dates for evaluation of VIEKIRA XR in the pediatric patients will be aligned with those for VIEKIRA PAK (NDA 206619).

The goal of the pediatric study is to investigate the pharmacokinetic parameters, safety and efficacy in the defined pediatric population.

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

*If not a PMR, skip to 4.*

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

This PMR will be completed in conjunction with the iPSP and PREA PMR for VIEKIRA PAK (NDA 206619). Primary pharmacokinetics and safety of ombitasvir, paritaprevir, and ritonavir will be established (b) (4)

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)

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

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)

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- Other

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

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

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

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

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**PMR/PMC Development Coordinator:**

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

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/s/  
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SUZANNE K STRAYHORN  
07/21/2016

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## 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)

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**Date of This Memorandum:** July 15, 2016  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 208624  
**Product Name and Strength:** Viekira XR  
(dasabuvir, ombitasivir, paritaprevir, and ritonavir) extended-release Tablets  
200 mg/8.33 mg/50 mg/33.33 mg  
**Submission Date:** July 11, 2016  
**Applicant/Sponsor Name:** Abbvie  
**OSE RCM #:** 2015-2346-1  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

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#### 1 PURPOSE OF MEMO

Abbvie has submitted the revised full prescribing information (FPI), carton, and container label (Appendix A) for Viekira XR in response to recommendations we made during a previous label and labeling review.<sup>1</sup> Thus, the Division of Antiviral Products (DAVP) requested that we review the revised FPI, label and labeling to determine if it is acceptable from a medication error perspective.

#### 2 CONCLUSIONS

<sup>1</sup> Calderon M. Label and Labeling Review for Viekira XR (NDA 208624). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 June 7. 32 p. OSE RCM No.: 2015-2346.

The revised carton labeling (monthly and weekly wallet pack), container label (daily dose wallet pack), <sup>(b)(4)</sup> and FPI have addressed all of our concerns and recommendations and are acceptable from a medication error perspective. We have no further recommendations.

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MONICA M CALDERON  
07/15/2016

BRENDA V BORDERS-HEMPHILL  
07/15/2016



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

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

## MEMORANDUM OF ELECTRONIC CORRESPONDENCE

**NDA:** 208624

**Drug:** Dasabuvir/ombitasvir/paritaprevir/ritonavir extended release tablets  
(200 mg / 8.33 mg / 50 mg / 33.33 mg)

**Date:** July 1, 2016

**To:** Sherie Masse, Director, Regulatory Affairs

**Applicant:** AbbVie, Inc.

**From:** Suzanne Strayhorn, Regulatory Project Manager

**Subject:** All Container Labels, Carton Labeling and Tips Card

Please refer to your submission dated September 28, 2015, which included draft carton and container labeling.

We have reviewed your submissions and have the following recommendations:

**A. All Container Labels, Carton Labeling, and (b)(4)**

1. The statement of strength for this product should reflect the strength of the individual active ingredients contained in each tablet. Thus, replace the strength statement appearing below the "TRADENAME" that reads (b)(4) with "200 mg/8.33 mg/50 mg/33.33 mg" to mitigate dosing errors.
2. Revise the established name to the following, "(dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets" to be consistent with the product title in the Highlights section of the USPI.
3. Replace "TRADENAME" with the conditionally acceptable proprietary name, Viekira XR.

**Viekira XR**

(dasabuvir, ombitasvir, paritaprevir, and ritonavir)  
Extended-Release Tablets

200 mg / 8.33 mg / 50 mg / 33.33 mg

4. Revise the statement regarding the content of each tablet to read, “Each VIEKIRA XR tablet contains 200 mg of dasabuvir equivalent to 216 mg of dasabuvir sodium monohydrate, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir”.
5. Add the following statement to the Principal Display Panel, “Do not split, crush or chew tablets”, to be consistent with the FPI.

**B. Container Label (Daily dose wallet pack)**

1. The lot number and expiration date are required on the immediate container per 21 CFR 201.10(i) and 21 CFR 201.17, respectively. Add both to the back panel of the packaging.
2. Revise the daily treatment instructions from, ‘Take all 3 tablets at the same time with a meal’ to ‘Take all 3 tablets once daily at the same time with a meal’ to mitigate the risk for errors identified in the Labeling Comprehension Supplementary Round of testing.

**C. Carton Label (Monthly wallet pack)**

1. The net quantity statement does not appear on the Principal Display Panel (PDP). Per Office of Pharmaceutical Quality (OPQ), add the following statement, “This carton contains 84 Tablets packaged as follows: 4 weekly cartons of therapy. Each weekly carton contains 21 tablets in 7 wallets of 3 tablets each.”, to the PDP for clarity and ensure it appears away from the product strength statement and with less prominence.

**D. Carton Label (Weekly wallet pack)**

1. The net quantity statement does not appear on the PDP. Per Office of Pharmaceutical Quality (OPQ), add the following statement, “This carton contains 21 Tablets packaged as follows: 7 wallets for 1 week of treatment. Each wallet contains 3 tablets”, on the PDP for clarity and ensure it appears away from the product strength statement and with less prominence.

(b)(4)

(b) (4)

**Please provide the revised labeling for review by July 8, 2016.**

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact me at (240) 402-4247 or (301) 796-1500.

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Suzanne Strayhorn, MS  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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SUZANNE K STRAYHORN  
07/01/2016

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

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

**Memorandum**

**Date:** June 20, 2016

**To:** Suzanne Strayhorn, Regulatory Project Manager  
Division of Antiviral Products

**From:** Jessica Fox, PharmD, RAC, Regulatory Review Officer  
Office of Prescription Drug Promotion

**Subject:** NDA 208624 – VIEKIRA XR (dasabuvir, ombitasvir,  
paritaprevir, and ritonavir) tablets, for oral use

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As requested in the Division of Antiviral Products' (DAVP) consult dated November 18, 2015, the Office of Prescription Drug Promotion (OPDP) has reviewed the VIEKIRA XR prescribing information, Medication Guide, and carton/container labeling.

OPDP reviewed the proposed substantially complete versions of the prescribing information sent via email by DAVP on June 8, 2016 (attached below for reference), and has no comments at this time.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the Medication Guide on June 17, 2016.

OPDP reviewed the proposed carton/container labeling submitted by the sponsor with the original submission (SDN 1) on September 28, 2015, and has no comments at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or Jessica.Fox@fda.hhs.gov.

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JESSICA M FOX  
06/20/2016

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

**PATIENT LABELING REVIEW**

Date: June 17, 2016

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

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

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Jessica Fox, PharmD, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir)

Dosage Form and Route: extended-release tablets, for oral use

Application Type/Number: NDA 208624

Applicant: AbbVie Inc.

## 1 INTRODUCTION

On September 28, 2015, AbbVie Inc. submitted for the Agency's review an original New Drug Application (NDA) 208624 for VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets. With this submission, AbbVie seeks approval of a new formulation of the components that constituted VIEKIRA PAK to a new single dosage tablet form, to allow for a once a day dosing regimen. VIEKIRA PAK (NDA 206619) was originally approved by the Agency on December 19, 2014 and contains separate tablets co-packaged as ombitasvir/ paritaprevir/ ritonavir tablets, and dasabuvir tablets. The Applicant plans to replace VIEKIRA PAK following approval of this NDA. The proposed indication for VIEKIRA XR is for the treatment of adult patients with chronic hepatitis C virus (HCV):

- genotype 1b infection without cirrhosis or with compensated cirrhosis
- genotype 1a infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin

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 November 18, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets.

## 2 MATERIAL REVIEWED

- Draft VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets MG received on September 28, 2015 and revised on November 2, 2015, and received by DMPP on June 9, 2016.
- Draft VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets MG received on September 28, 2015, and revised on November 2, 2015, and received by OPDP on June 8, 2016.
- Draft VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets Prescribing Information (PI) received on September 28, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on June 9, 2016.
- Draft VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets Prescribing Information (PI) received on September 28, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on June 8, 2016.
- Approved VIEKIRA PAK (ombitasvir, paritaprevir, ritonavir tablets; dasabuvir tablets) comparator labeling dated April 22, 2016.

### **3 REVIEW METHODS**

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible.
- ensured that the MG is consistent with the Prescribing Information (PI).
- removed unnecessary or redundant information.
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language.
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
- ensured that the MG is consistent with the approved comparator labeling where applicable.

### **4 CONCLUSIONS**

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/  
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SHARON R MILLS  
06/17/2016

JESSICA M FOX  
06/17/2016

BARBARA A FULLER  
06/17/2016

LASHAWN M GRIFFITHS  
06/17/2016

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## LABEL AND LABELING REVIEW

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)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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**Date of This Review:** June 7, 2016

**Requesting Office or Division:** Division of Antiviral Products (DAVP)

**Application Type and Number:** NDA 208624

**Product Name and Strength:** Viekira XR  
(dasabuvir, ombitasivr, paritaprevir, and ritonavir) extended-release Tablets  
200 mg/8.33 mg/50 mg/33.33 mg

**Product Type:** Multi-ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Abbvie, Inc.

**Submission Date:** September 28, 2015

**OSE RCM #:** 2015-2346

**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS

**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

**DMEPAT Deputy Director:** Irene Chan, PharmD, BCPS

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## 1 REASON FOR REVIEW

Abbvie submitted a new drug application (NDA 208624) for Viekira XR (dasabuvir extended-release, ombitasvir, paritaprevir, and ritonavir) Tablets for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection with or without ribavirin. Abbvie plans for Viekira XR to eventually replace Viekira Pak after a short duration of overlap on the market. The Division of Antiviral Products (DAVP) requested that DMEPA evaluate the Applicant's proposed container labels, carton labeling, labeling comprehension study and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors.

## 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.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other- Labeling Comprehension Study	F
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a multi-ingredient, single-strength tablet available as dasabuvir 200 mg/ombitasvir 8.33 mg/paritaprevir 50 mg/ritonavir 33.33 mg. Three tablets will be packaged in a daily dose wallet pack, seven daily dose wallet packs are contained within a weekly carton, and four weekly cartons are packaged within a monthly carton for a 28 day supply. This packaging configuration is supported by the dosage and administration of this product. This packaging configuration is modeled after Abbvie's currently approved Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; copackaged with dasabuvir tablets), NDA 206619 (see Appendix G). The proposed product differs from Viekira Pak by the total number of tablets taken daily and in the frequency of administration. Viekira XR is administered as three tablets once daily with food versus Viekira Pak which is administered twice daily (3 tablets in the morning and 1 tablet in the evening) with food. We performed a risk assessment of the proposed container label and carton labeling, labeling comprehension study results, and the full

prescribing information (FPI) to identify deficiencies that may lead to medication errors and areas of improvement.

### **FPI- Dosage and Administration Section**

We note the proposed FPI clearly states the daily dosing and administration of Viekira XR in the Dosage and Administration section. However, to provide clarification regarding the strength of each active ingredient contained in each tablet throughout the FPI, we provide recommendations in Section 4.1. We also recommend the FPI be updated to reflect the conditionally acceptable proprietary name, Viekira XR.

### **Labeling Comprehension Study**

Abbvie performed a labeling comprehension study to validate that the intended user group can accurately comprehend the safe and effective self-administration of HCV 3QD regimen (i.e. Viekira XR).

Participants (n=25) diagnosed with HCV who had received treatment, were currently receiving treatment, or were not receiving treatment representing a range of socioeconomic and education levels were included in the study. Each participant was given one Daily Dosing Wallet and asked a series of questions to determine their understanding of the three critical steps (Appendix F.3) required for a user to administer the medication successfully.

Success was defined as participants correctly verbalizing all three critical steps. In the event that the participant did not initially mention all of the critical steps, a series of label comprehension questions were asked to further probe his/her understanding of the packaging. Failure was defined as participants failing to verbalize or verbalizing incorrectly any of the three critical steps in the administration process. Root cause analysis and failure analysis occurred after all comprehension questions were asked.

Eight out of fifteen participants in the Initial Round of testing failed to comprehend that all three tablets must be taken together at one time. Thus, modifications were made to the design of the packaging to clarify all three tablets are to be taken at one time (Appendix F.4). A Supplementary Round of testing was conducted, wherein one out of ten participants failed to successfully comprehend that only one daily dosing wallet is to be taken each day. Abbvie concluded the root cause of this failure was a test artifact and was not indicative of a pattern of preventable use error. Therefore, they did not recommend any additional changes to the instructions as they did not believe they would further improve label comprehension. DMEPA does not agree this failure is not indicative of a pattern of preventable use error. We determined that an additional change to the daily dosing wallet may further mitigate the risk associated with this failure. We provide recommendations in Section 4.2.

### **Container Label, Carton Labeling, and Full Prescribing Information (FPI)**

We evaluated the proposed daily dose pack label, weekly carton labeling, and monthly wallet labeling. The color scheme is slightly different from Abbvie's currently marketed Viekira Pak and

Abbvie has proposed a Market Conversion Strategy <sup>1</sup> to inform patients and prescribers of the availability of Viekira XR while Viekira Pak continues to be in distribution to help minimize confusion between both drugs. We determined there is adequate labeling differentiation, which sufficiently addresses our concern for product selection error. Of note, Viekira XR contains the same active ingredients as Viekira Pak. If a patient were to receive the wrong product, the patient will ultimately still be receiving the same total amount of each active ingredient per day. Although the total number of tablets and frequency of administration differs, the dosing and administration of each respective medication is depicted on the daily dosing wallet for each product, thereby mitigating improper dosing errors should a product selection error occur.

The weekly carton labeling provides dosing instructions in addition to the days of the week to help serve as a tool to remind patients as to when they last took their medication. The proposed monthly and weekly carton labeling and daily dose wallet label currently list the established name as “dasabuvir ER; ombitasvir, paritaprevir, and ritonavir IR” with the modified release properties abbreviated versus spelled out, which may lead to confusion. Also of note, the net quantity is missing from the Principal Display Panel (PDP) and the strength appearing below the tradename on the monthly carton, weekly carton, and daily dose wallet is provided as the sum total strength of all three tablets (b)(4) versus the strength of each individual tablet (200 mg/8.33 mg/50 mg/33.33 mg) which may result in strength and dosing confusion. We communicated these concerns to Office of Pharmaceutical Quality (OPQ) and the DAVP Associate Director for Labeling (ADL), and we provide our collaborative recommendations in Section 4.2 to clarify the (b)(4) properties of the individual active ingredients in the established name and any confusion regarding the net quantity contained in the monthly carton and the strength of each individual tablet.

We also note the container label on the daily dosing wallet (b)(4) provides pictorials and diagrams to help assist patients in taking their medications correctly once daily. However, we recommend the frequency of dosing is added to the dosing instructions to help minimize any confusion regarding how many tablets and daily dosing wallets should be taken once daily to address the failure seen in the Labeling Comprehension Supplementary Round of testing. (b)(4)

(b)(4) The expiration date and lot number are also required minimum information that should be included on the container label. We provide recommendations in Section 4.2. These can be implemented without requiring additional HF testing.

#### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that an additional change to the daily wallet instructions may help to mitigate wrong frequency errors identified during the labeling comprehension study. The container label and carton labeling can also be revised to improve readability, to mitigate

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<sup>1</sup> Calderon M. Label Comprehension Study Review (dasabuvir, ombitasvir, paritaprevir, and ritonavir) IND 122839. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 May 28. RCM No.: 2014-2344.

wrong dose and frequency errors, and to add lot number and expiration date on the immediate container. The labels and labeling should be updated with the conditionally acceptable proprietary name, Viekira XR, where applicable. See section 4.1 and 4.2, below for our recommendations. These revisions can be implemented without requiring additional HF testing.

#### **4.1 RECOMMENDATIONS FOR THE DIVISION**

##### Full Prescribing Information

1. We provide recommended revisions to the Division’s working FPI document (see Appendix G) to revise the D&A section, Dosage form and Strengths, How Supplied and Highlights section to provide the unit of measure for each strength of each active ingredient for improved readability.
2. Replace “TRADENAME” with the conditionally acceptable proprietary name, Viekira XR.

#### **4.2 RECOMMENDATIONS FOR ABBVIE, INC**

We recommend the following be implemented prior to approval of this NDA. These revisions can be implemented without requiring the submission of additional HF testing data.

##### **A. All Container Labels, Carton Labeling, and (b)(4)**

1. The statement of strength for this product should reflect the strength of the individual active ingredients contained in each tablet. Thus, replace the strength statement appearing below the “TRADENAME” that reads “(b)(4)” with “200 mg/8.33 mg/50 mg/33.33 mg” to mitigate dosing errors.
2. Per Office of Pharmaceutical Quality (OPQ) and the DAVP Associate Director for Labeling (ADL), revise the established name to the following, “(dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets” to be consistent with the product title in the Highlights section.
3. Replace “TRADENAME” with the conditionally acceptable proprietary name, Viekira XR.

##### **B. Container Label (Daily dose wallet pack)**

1. The lot number and expiration date are required on the immediate container per 21 CFR 201.10(i) and 21 CFR 201.17, respectively. Add both to the back panel of the packaging.
2. Revise the daily treatment instructions from, ‘Take all 3 tablets at the same time with a meal’ to ‘Take all 3 tablets once daily at the same time with a meal’ to mitigate the risk for errors identified in the Labeling Comprehension Supplementary Round of testing.

**C. Carton Label (Monthly wallet pack)**

1. The net quantity statement does not appear on the Principal Display Panel (PDP). Per Office of Pharmaceutical Quality (OPQ), add the following statement, “This carton contains 84 Tablets packaged as follows: 4 weekly cartons of therapy. Each weekly carton contains 21 tablets in 7 wallets of 3 tablets each.”, to the PDP for clarity and ensure it appears away from the product strength statement and with less prominence.

**D. Carton Label (Weekly wallet pack)**

1. The net quantity statement does not appear on the PDP. Per Office of Pharmaceutical Quality (OPQ), add the following statement, “This carton contains 21 Tablets packaged as follows: 7 wallets for 1 week of treatment. Each wallet contains 3 tablets”, on the PDP for clarity and ensure it appears away from the product strength statement and with less prominence

(b)(4)

(b) (4)

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Viekira XR that Abbvie, Inc submitted on September 28, 2015.

<b>Table 2. Relevant Product Information for Viekira XR and the Listed Drug</b>		
<b>Product Name</b>	<b>Viekira XR</b>	<b>Viekira Pak</b>
<b>Initial Approval Date</b>	N/A	December 19, 2014
<b>Active Ingredient</b>	dasabuvir, ombitasvir, paritaprevir, and ritonavir	Dasabuvir, ombitasvir, paritaprevir, ritonavir
<b>Indication</b>	Treatment of genotype 1 chronic HCV including those with compensated cirrhosis in combination with or without ribavirin.	Treatment of chronic HCV genotype 1 infection with or without ribavirin.
<b>Route of Administration</b>	Oral	Oral
<b>Dosage Form</b>	Tablets	Tablets
<b>Strength</b>	200 mg/8.33 mg/50 mg/33.33 mg	dasabuvir: 250 mg ombitasvir, paritaprevir, ritonavir: 12.5 mg/75 mg/50 mg
<b>Dose and Frequency</b>	Three tablets once daily	<u>Morning:</u> Two tablets of ombitasvir, paritaprevir, ritonavir + One tablet of dasabuvir with food (in the morning) <u>Evening:</u> One tablet of dasabuvir with food
<b>How Supplied</b>	Monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child resistant daily dose pack contains three tablets.	Monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child resistant daily dose pack contains four tablets: two ombitasvir, paritaprevir, ritonavir tablets, 12.5 mg/75 mg/50 mg and two tablets of dasabuvir 250 mg
<b>Storage</b>	Store at or below 30°C (86°F).	Store at or below 30°C (86°F).

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On April 15, 2015, we searched the L:drive and AIMS using the terms, Viekira Pak to identify reviews previously performed by DMEPA.

### **B.2 Results**

We evaluated the most recent label and labeling review for Viekira Pak<sup>2</sup>, since the packaging configuration and product characteristics are similar to the proposed product. There were no recommendations from our previous review to inform our review of the proposed product's label and labeling.

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<sup>2</sup> Calderon M. Label and Labeling Review for Viekira Pak NDA 206619/S-009. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Jan 25. RCM No.: 2015-2477.

## **APPENDIX F. LABELING COMPREHENSION STUDY - EXCERPTS FROM SUBMISSION**

### **F.1 Study Design**

The primary objective of the labeling comprehension study was to validate that the intended user group can accurately comprehend the safe and effective self-administration of HCV 3QD regimen.

### **F.2 Study Population**

- 25 total patient participants with HCV
  - Initial Round (n=15, aged 18 to 75 years)
    - Received treatment or currently receiving treatment
  - Supplementary round (n=10, aged 18 to 75 years)
    - Received treatment or currently receiving treatment

### **F.3 Design**

For each participant, the moderator initiated testing by first presenting the situational context. Then the moderator observed participant behavior and evaluated answers to questions aimed at evaluating participant comprehension of the correct dosing. All participants were untrained.

#### Definition of Performance Success/Failures

- Success: Participants correctly verbalized all critical steps in the administrative process.
  - Take three tablets all at once
  - Take with food
  - Take one package daily
- Fail: Participant failed to verbalize or verbalized in correctly any of the three critical steps in the administration process.

Root cause probing and failure analysis occurred after all comprehension questions were asked.

#### Data collected:

- Successful comprehension of critical steps
- Comprehension failures/errors and reported root causes
- Unanticipated comprehension errors observed or indicated by participants during testing
- Subjective participant feedback through open-ended and closed questioning

#### F.4 Labeling Comprehension Results

In the Initial Round of testing, 7 of 15 (47%) participants who received the Daily Dosing Wallet correctly comprehended the following for critical steps: take three tablets at one time, with food, and daily.

**Table 3. Summary of Initial Round of Testing Critical Step Successes**

	Critical Comprehension Steps			Overall Success
	Dose (three dasabuvir, ombitasvir, paritaprevir and ritonavir (3QD) tablets) (Take 3 tablets all at once)	Food (Take with solid food)	Daily (Take package daily)	
Wallet N = 15	7 (47%)	15 (100%)	15 (100%)	7 (47%)

**Table 5. Daily Dosing Wallet detailed analysis of failures observed on critical steps during the Initial Round of testing**

Participant (P#)	Reason(s) for Failure	Root Cause	Detailed Explanation
2	Initially stated that he would take one tablet, but later said he would take whatever the daily dose was, and the packaging led him to believe the daily dose would be 3 tablets at once.	Negative transfer – Participant's current medication is one tablet per day.	Looking closer at the Daily Dosing Wallet packaging the participant later realized on his own that all 3 tablets must be taken with food once a day.  When asked if there was anything that caused him to be concerned or make him feel like he was about to make a mistake, the participant said that he is currently on medication that is one pill daily, and so he initially associated that a daily dose is one pill.
4	Would take one tablet with each meal throughout the day.	Mental Model/Negative Transfer – Not accustomed to taking so many tablets at once. Currently takes one pill per day for hypertension.	The participant indicated that the picture indicating the dosing instructions was not clear and that it did not indicate the time of day to take the medication or whether the tablets should be staggered or taken all at once. He wavered back and forth, but finally decided that 3 tablets across the day would be safer than 3 tablets at the same time.  The participant currently takes one pill once per day, and assumed he would stagger the 3 tablets throughout the day. While he said he was confident in his assessment of the labeling, he would still call his doctor to confirm the correct dosing strategy.

Participant (P#)	Reason(s) for Failure	Root Cause	Detailed Explanation
7	Would take one tablet with each meal throughout the day.	<b>Mental Model –</b> Assumed that 3 tablets with food would mean one pill with each meal spread throughout the day.	With medication to treat her Hepatitis C she thinks she needs to space it out and would want a constant level of the drug in her system. She made an analogy to insulin, saying that you don't want to have too much or too little in your body and that you don't drink a gallon of water in the morning, but might drink a gallon of water over the course of the day.  She would get answers from her doctor before making any assumptions and doesn't take any medication lightly and discusses thoroughly with her doctor. Expects that doctors might prescribe different dosing strategies for different patients.  The label was not clear that she should take all 3 tablets at the same time. Participant expected that the Daily Dosing Wallet would explicitly instruct to take all 3 tablets at the same time if that was the case.
8	Initially said he would take the tablets according to how his current medication is dosed. However, looking at the picture on the inside of the wallet's top flap, he realized it was all 3 tablets at once daily.	<b>Negative transfer/Test artifact –</b> Participant misunderstood the task and thought he was to describe how he would take these tablets based on his experience with his current medication.	Initially the participant was confused by the task scenario and thought that he was supposed to take this medication as he takes his current medication. After the moderator clarified that this was a different medication than the one he is currently taking, the participant immediately realized that he needed to take the HCV 3QD medication differently and saw the instructions to take all 3 tablets at one time each day on the inside of the wallet's top flap.

Participant (P#)	Reason(s) for Failure	Root Cause	Detailed Explanation
9	Would take one tablet with each meal throughout the day. Not totally confident as she initially thought to take all 3 tablets at once. She would feel more confident once her doctor told her how to take it.	Mental Model – Thought taking all 3 tablets at once would be excessive.	If the participant was at home without instructions from the doctor or pharmacy she stated she would take one pill 3 times a day. The participant admitted that she was confused by the picture. She stated that the picture on the inside of the top flap suggested to her that she should take all 3 tablets at once. Even though the picture inside the top flap of the wallet was clear she still felt like she should not take all tablets at once. The participant stated that she would call her doctor and that would give her the confidence necessary to take all 3 tablets at the same time. She also suggested that the packaging should more clearly state that all 3 tablets are intended to be taken together at one time. She said she would rely on the prescription label and might take advantage of the phone number on the daily wallet package to gain further clarification.
12	Initially thought to take only one pill, but after closer inspection of the daily treatment illustration realized he needed to take all 3 tablets at once daily.	Test Artifact – Participant stated that he typically reads all of the additional materials that come with prescription medications.	During warm-up questioning the participant stated that when bringing home a new prescription medication he typically reads all of the inserts and prescribing information as well as any material from the pharmacy. The lack of these materials in the test environment caused the participant to second guess whether or not he had enough information to decide what the correct dose would be. When relying strictly on the Daily Dosing Wallet packaging he was able to identify the correct dose.

Participant (P#)	Reason(s) for Failure	Root Cause	Detailed Explanation
13	She initially stated that she would take one tablet with each meal throughout the day because she had no other information to base her decision on. When the moderator asked her what she would take based on the packaging, she stated that she would take all three at once.	<b>Test Artifact -</b> Participant stated that she typically reads all of the additional materials that come with prescription medications.	This participant stated that she usually reads all of the information when receiving a new prescription medication before leaving the pharmacy so that she can ask any questions face-to-face with the pharmacist. The participant expected that there would be a pharmacy label on the medication in case there were special instructions for how she was supposed to take the medication. When asked to rely only on the Daily Dosing Wallet packaging for this information it was clear from the illustration the participant stated that she was to take all 3 tablets at one time with food daily.
15	Would take one tablet with each meal throughout the day.	<b>Mental Model –</b> Trauma from a past experience when she took many supplements at once, up to 10 pills at a time, which resulted in a hospitalization.	Frightened to take 3 tablets at one time without clarification other than the instructional picture on the inside flap of the daily wallet. She is concerned about negative side effects of medications for treating Hepatitis C and thinks that 3 tablets at a time is too much to put in your body due to her past negative experience. She has not treated her Hepatitis C as she has been waiting for new medications with fewer side effects.

The Applicant determined most of the miscomprehension was associated with the picture on the inner flap of the Daily Dosing Wallet. The instruction ‘Three tablets + food’ was understood to mean one tablet with each meal throughout the day. Three participants expected to speak with a healthcare provider to clarify any confusion, most often their doctor.

Participants suggested adding wording around the inner flap of the daily dosing wallet to read, “take all three tablets together with a meal” or “take all three with breakfast” when asked what could be changed to make the instructions more clear.

In response to the failures listed above, minor modifications were made to the Daily Dosing Wallet package instructions to improve comprehension that all three tablets were to be taken at the same time.

During Supplementary Round of testing after Daily Dosing Wallet instructions were modified to clarify dosing regimen, 9 of 10 (90%) participants successfully comprehended all critical steps.

**Table 4. Summary of Supplementary Round of Testing Critical Step Successes**

	Critical Comprehension Steps			Overall Success
	Dose (three dasabuvir, ombitasvir, paritaprevir and ritonavir (3QD) tablets) (Take 3 tablets all at once)	Food (Take with food)	Daily (Take package daily)	
<b>Wallet</b> N = 10	10 (100%)	10 (100%)	9 (90%)	9 (90%)

**Table 6. Supplementary Testing of Daily Dosing Wallet detailed analysis of failure observed on critical steps**

Participant (P#)	Reason(s) for Failure	Root Cause	Detailed Explanation
S4	It was unclear to the participant that only 1 Daily Dosing Wallet was to be taken each day.	<p><b>Test Artifact-</b> He was given one Daily Dosing Wallet without the context of the full months of medication (A month's box with four weekly boxes with each of those boxes containing 7 Daily Dosing Wallets).</p> <p><b>Package Design/Terminology-</b> The text 'Daily Treatment Instructions' did not translate to take one Daily Dosing Wallet per day.</p>	Participant S4 said he would take two Daily Dosing Wallet packs a day per his doctor's instructions. When asked about where he got the doctor's instruction, he admitted to storytelling to fill in information that was missing. He articulated that the package did not contain adequate information about how many daily dosing wallets to take. The participant mentioned that he would call the doctor or prescription place (he may have been referring to the pharmacist or manufacturer), during probing, to get the correct dosing amount. When the moderator reread "You filled your prescription and you brought home a month's of medication from the pharmacy. You removed one of these [wallet] packages from one of the four weekly boxes", the participant realized that the Daily Dosing Wallet contained one day's worth of medication.

The Applicant determined this failure was primarily due to this specific participant 'storytelling' to fill in information that will be present in multiple formats in a real-world scenario, this is considered a test artifact. The usability of weekly and monthly cartons was previously validated in the Viekira Pak human factors study and those designs remain consistent for the same intended users for HCV 3QD regimen.

**Applicant Conclusion**

The study demonstrated that participants correctly comprehended HCV 3QD packaging messaging for all three critical steps: take all three tablets in the Daily Dosing Wallet and one time, with food, daily. Moreover, the results indicate that there is not a pattern of preventable comprehension error. No additional instruction changes were identified that could further improve label comprehension.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>3</sup> along with postmarket medication error data, we reviewed the following Viekira XR labels and labeling submitted by Abbvie, Inc on September 28, 2015.

- FPI
- Container label
- Carton labeling

FPI- Highlights, Dosage and Administration section, Dosage Forms section, and How Supplied/Storage and Handling section

#### -----DOSAGE AND ADMINISTRATION-----

- Recommended dosage: Three tablets (b) (4)  
meal (b) (4) taken once daily with a (b) (4)

#### -----DOSAGE FORMS AND STRENGTHS-----

Tablets: Dasabuvir, ombitasvir, paritaprevir, and ritonavir: 200 mg/8.33 mg/50 mg/33.33 mg (3)

### 2 DOSAGE AND ADMINISTRATION

(b)(4)

### 3 DOSAGE FORMS AND STRENGTHS

(b)(4)

tablets are pale yellow-colored, film-coated, oblong shaped, debossed with “3QD” on one side.

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<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

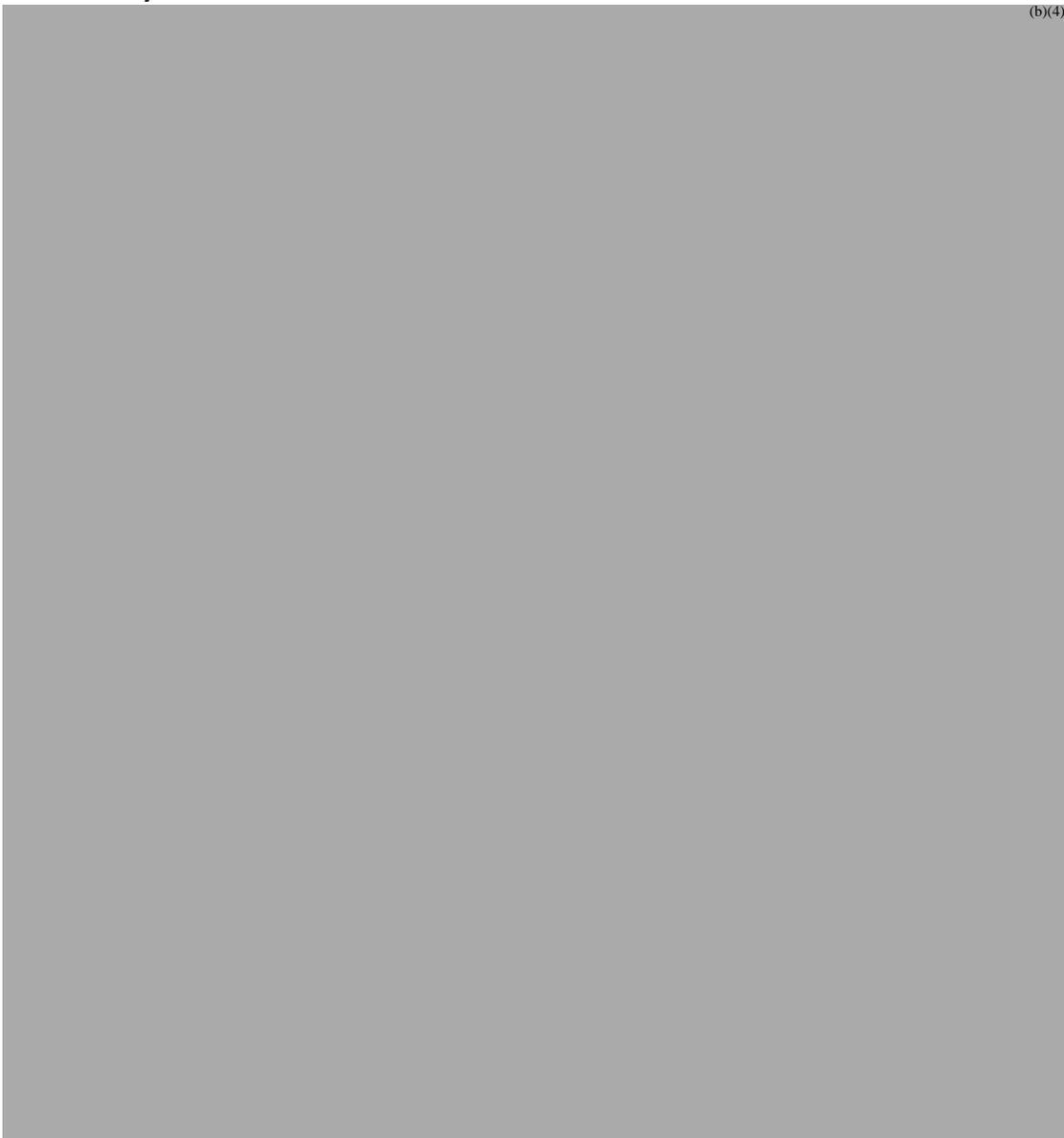
Each child-resistant daily dose pack contains three tablets. The NDC number is 0074-0063-28.

Dasabuvir, ombitasvir, paritaprevir, and ritonavir 200 mg/8.33 mg/50 mg/33.33 mg tablets are pale yellow-colored, film-coated, oblong shaped, debossed with “3QD” on one side.

Store at or below 30°C (86°F).

### G.2 Label and Labeling Images

#### Daily Wallet Pack



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MONICA M CALDERON  
06/07/2016

BRENDA V BORDERS-HEMPHILL  
06/08/2016

IRENE Z CHAN  
06/13/2016

M E M O R A N D U M

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

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DATE: March 23, 2016

TO: Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products (DAVP)  
Office of Antimicrobial Products (OAP)  
Office of New Drugs (OND)

FROM: Xiaohan Cai, Ph.D. and Sripal R. Mada, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance  
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.  
Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance  
Office of Translational Sciences

SUBJECT: Review of EIR covering NDA 208624 for an  
analytical inspection conducted at AbbVie Inc.,  
North Chicago, IL

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**Recommendations:**

At the request of Division of Antiviral Products (DAVP), OND, Xiaohan Cai, Ph.D. and Sripal R. Mada, Ph.D. from the Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) audited the analytical portion of the following study at AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064 (AbbVie). We recommend that the data from the analytical portion of study M14-566 be accepted for further agency review.

Application	Study	Drug Product	Sponsor	Recommend
NDA 208624	M14-566	Dasabuvir/Ombitasvir/ Paritaprevir/ Ritonavir 200mg/8.33mg/50mg/ 33.33mg fixed-dose combination tablets	AbbVie, Inc.	<b>Acceptable</b>

**M14-566:** "A Comparison of the Bioavailability of Dasabuvir, Ombitasvir, ABT-450 and Ritonavir Combination Regimen Bilayer Tablets (Film-Coated Quad ER-12: Dasabuvir/Ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) and the Phase 3 Clinical Reference Regimen (Ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD + Dasabuvir 250 mg BID) in Healthy Subjects"

**Dates of sample analysis:** 09/25-12/11/2014

**Inspection:**

The inspection of the analytical portion of study M14-566 was conducted at AbbVie from February 08-12, 2016. The audit included a thorough review of method validation and study records, examination of facility, equipment, electronic laboratory notebook system, and interviews and discussions with the firm's management and staff. Following the inspection, Form FDA 483 was issued to AbbVie (Attachment 1). The firm responded to Form FDA 483 on March 03, 2016 (Attachment 2) and March 22, 2016. The Form FDA 483, the firm's response to Form FDA 483, and our evaluation follow.

**OBSERVATION 1:**

**During the method validation to measure ritonavir, dasabuvir, ABT-450, dasabuvir M1 metabolite and ombitasvir in human plasma, the firm failed to use freshly spiked calibrators in autosampler, freeze/thaw and room temperature stability experiments.**

**Firm's Response:** AbbVie acknowledged that freshly spiked calibrators were not utilized for autosampler, freeze/thaw, and room temperature stability evaluations. Following the inspection, AbbVie repeated above experiments using freshly spiked calibrators and submitted the data in their response to 483. AbbVie stated that the results confirmed the conclusion of autosampler, freeze/thaw, and room temperature stability from previously reported data. As a corrective action, AbbVie will update the SOP to require use of fresh calibrators in all stability experiments.

**OSIS Evaluation:** The firm has re-established autosampler, freeze/thaw, and room temperature stability for all analytes for 70 hours, 5 cycles, and 15 hours, respectively. Although the re-established duration of room temperature stability is shorter than the one evaluated during the initial method validation, the longest duration that study samples remained on the benchtop was within the re-established stability for all analytes. The proposed corrective action is adequate for future studies.

Therefore, this observation does not impact the integrity of the study data.

**OBSERVATION 2:**

**The firm failed to evaluate selectivity of the bioanalytical method to quantify ritonavir, dasabuvir, ABT-450, dasabuvir M1 metabolite and ombitasvir in human plasma. Specifically, the study samples were analyzed for the mentioned five analytes, but the interference from an analyte on another among the five analytes and five internal standards was not evaluated.**

**Firm's Response:** AbbVie acknowledged that the interference of an analyte to other analytes or internal standards was not evaluated for ritonavir, dasabuvir, ABT-450, dasabuvir M1 and ombitasvir in human plasma. After the inspection, AbbVie evaluated the interference on each analyte by adding other four analytes into a blank sample at ULOQ level and all five internal standards during extraction. The % interference was evaluated using the analyte peak area of the absent analyte peak compared to that analyte peak area of the LLOQ standard. Results from the interference test showed insignificant interferences (< 20% of LLOQ peak area) for all five analytes. As a corrective action, AbbVie will update the SOP to require evaluation of interference when multiple analytes are quantitated in a single method.

**OSIS Evaluation:** The firm has evaluated interference on one analyte from other analytes and internal standards and the results showed insignificant interference for all five analytes. The proposed corrective action is adequate for future studies. Therefore, this observation does not have impact on the integrity of the study data.

**OBSERVATION 3:**

**Study samples were not stored in a secure and controlled environment. Specifically, subject plasma samples were stored in unlocked -20 °C freezers located in an unsecured common area in the analytical facility.**

**Firm's Response:** In their response to the Form FDA 483, AbbVie promised to implement the following corrective actions: 1) Sample receiving freezers will be moved to a separate room, the access to which will be limited to appropriate emergency maintenance and sample receiving personnel; 2) Freezer rooms within the bioanalysis laboratory will have a separate secured access, allowing the access of personnel only from bioanalysis, sample receiving, and appropriate emergency maintenance.

**OSIS Evaluation:** During the inspection, we reviewed source documents for sample arrival and subject sample analysis and did not find any discrepancy. Therefore, the above finding does not impact on the integrity of the study data. AbbVie's response is acceptable for future studies. After implementation, the corrective actions would provide physical security for study samples stored in freezers.

**Conclusion:**

Based on the observations above, these OSIS reviewers conclude that the data from the audited study are reliable. Therefore, these reviewers recommend that the analytical portion of the audited study be accepted for further Agency review.

Xiaohan Cai, Ph.D.  
OSIS, DGDBE

Sripal R. Mada, Ph.D.  
OSIS, DGDBE

**Final Site Classification:**

**VAI - AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064**  
**FEI: 3009751352**

cc:  
OSIS/Kassim/Taylor/Miller/Nkah/Fenty-Stewart/Kadavil  
OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Cai/Mada  
OSIS/DNDBE/Bonapace/Dasgupta  
OND/OAP/DAVP/Birnkrant/Strayhorn

Draft: XC 03/17/2016; XC 03/21/2016  
Edit: SRM 03/21/2016; YMC 03/22/2016; JC 03/23/2016  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL  
SITES/Abbvie, North Chicago, IL/  
NDA 208624\_Dasabuvir\_Ombitasvir\_ABT-450\_Ritonavir

OSI file# BE7017

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SEONGEUN CHO  
03/24/2016

MEMORANDUM

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

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DATE: January 8, 2016

TO: Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products (DAVP)  
Office of Antimicrobial Products (OAP)  
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.  
Visiting Associate  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.  
Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR covering Study M14-566 submitted to NDA  
208624 conducted at Celerion Inc., Tempe, AZ

**Inspection Summary:**

At the request of the Division of Antiviral Products (DAVP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of bioavailability study M14-566 at Celerion Inc., Tempe, AZ. At the inspection close-out meeting, no significant deficiencies were observed and no form FDA 483 was issued. The final classification for this inspection is no action indicated (NAI). I recommend that the data for the clinical portion of **Study M14-566** be accepted for further agency review.

**Study Number:** M14-566

**Study Title:** "A Comparison of the Bioavailability of Dasabuvir, Ombitasvir, ABT-450 and Ritonavir Combination Regimen Bilayer Tablets (Film-Coated Quad ER-12: Dasabuvir/Ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) and the Phase 3 Clinical Reference Regimen

(Ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD +  
Dasabuvir 250 mg BID) in Healthy Subjects"

**Study Conduct:** August 1 - November 13, 2014

**Clinical Site:** Celerion Inc.  
2420 West Baseline Road  
Tempe, AZ 85283

The inspection of the clinical portion of the study was conducted by investigator Lakecha N. Lewis, at Celerion Inc., Tempe, AZ from December 7 - 17, 2015.

The current audit covered a review of study protocols and amendments, subjects' informed consent forms (ICFs), eligibility documents, screening logs, delegation logs, IP/study drug receipt, storage, accountability, pharmacy drug accountability records, administration/dosing and shipment records, IRB approvals, sponsor/monitoring correspondence, monitoring visit logs, laboratory result reports, hardcopy and electronic source records and electronic case report forms (eCRFs). No discrepancies were observed and there was no under-reporting of AEs. The site retained reserve samples for the study.

No significant issues were observed and no Form FDA 483 was issued at the conclusion of the inspection.

**Recommendations:**

Following review of the inspectional findings, the clinical data from the audited study conducted at Celerion Inc. were found to be reliable. Therefore, I recommend that the data for the clinical portion of Study M14-566 submitted to NDA 208624 be accepted for further agency review.

Yiyue Zhang, Ph.D.  
DNDBE, OSIS

**Final Classification:**

**Clinical**

**NAI:** Celerion Inc., Tempe, AZ

CC:

OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang

OTS/OSIS/DGDBE/Haidar/Skelly/Choi

OND/OAP/DAVP/Birnkrant/Strayhorn

ORA/PA-FO/LOS-DO/LOS-DIB/Lewis

Draft: ZY 1/6/2016

Edit: CB 01/08/2016

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/Celerion Inc., Tempe, AZ

BE File #: 7017

**FACTS: 11562622**

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YIYUE ZHANG  
01/08/2016

CHARLES R BONAPACE  
01/08/2016

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

**Application:** NDA 208624

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** dasabuvir, ombitasvir, paritaprevir and ritonavir, (200 mg / 8.33 mg /50 mg / 33.33 mg) fixed-dose combination tablets

**Applicant:** AbbVie, Inc.

**Receipt Date:** September 28, 2015

**Goal Date:** July 28, 2016

## **1. Regulatory History and Applicant's Main Proposals**

This PLR format review has been completed for a new NDA received from AbbVie Inc., for a fixed dose combination (FDC) tablet of dasabuvir, ombitasvir, paritaprevir, ritonavir (200 mg/ 8.33 mg/ 50 mg/ 33.33 mg), for treatment of patients with HCV, Genotype 1 (GT1).

This application is a new formulation of a previously approved product from AbbVie, with the trade name of Viekira Pak™ (*ref: NDA 206619, approved on 12/19/2014*). Viekira Pak™ consists of co-formulated ombitasvir/paritaprevir/ritonavir tablets (12.5 mg/75 mg/50 mg) co-packaged with dasabuvir (250 mg) tablets. With this new NDA application, AbbVie, Inc., is proposing to take the the 4 components of Viekira Pak™ and incorporate these into a single tablet, to allow for once daily dosing (3 tablets/per day).

For the draft labeling provided with this new NDA, the applicant has only slightly modified the language from the approved package insert for Viekira Pak™. The applicant has also incorporated the revisions reflecting PLLR. Finally the applicant is requesting a waiver to exceed the ½ page length requirement for the Highlights section of the label.

## **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**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

# Selected Requirements of Prescribing Information

## 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.

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### 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:**

- NO** 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 is requesting a waiver to 1/2 page HL section to allow for inclusion of additional product and safety information.

- 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 UPPER CASE 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. Headings in HL must be presented in the following order:

## Selected Requirements of Prescribing Information

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

\* RMC only applies to 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:**

#### 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:** *Year to be added upon NDA approval.*

#### Boxed Warning (BW) in Highlights

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

**Comment:** *No boxed warning proposed within applicants draft label.*

**N/A**

## Selected Requirements of Prescribing Information

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

**Comment:**

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

**Comment:**

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

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only 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:** *This is a new NDA submission and as such RMC changes in HL does not apply*

- 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:** *Not applicable as only single dosage form proposed- tablets.*

### Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

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: All contraindications in FPI are detailed in HL.

### Adverse Reactions in Highlights

- 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](http://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: Note: Medication Guide is proposed and therefore 3<sup>rd</sup> bullet is included in applicant proposed labeling.

### 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: Currently reads “Revised: X/201X”. Actual date will be added upon approval.

## Selected Requirements of Prescribing Information

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### 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:*
- N/A** 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:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 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.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 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:**

## Selected Requirements of Prescribing Information

- N/A** 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

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 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

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment: *Not applicable - known contraindications are listed*

#### 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: *Applicant has proposed modification to the above statement, to insert tradename of drug as follows "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of TRADENAME cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice." :*

- NO** 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.”

## Selected Requirements of Prescribing Information

**Comment:** *Post marketing adverse reaction of hypersensitivity reaction has been added, likely based on prior experience with Viekira Pak. However the above statement has not been included. Team to discuss if postmarketing information is to be included based on prior experience with Viekira Pak..*

### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 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:**

- YES** 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

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

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

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: TITLE OF WARNING

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

### 15 REFERENCES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE K STRAYHORN  
11/30/2015

ELIZABETH G THOMPSON  
12/01/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 208624	NDA Supplement #: Not Applicable (N/A) – not a supplement	Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
<b>Proprietary Name:</b> TBD (VIEKIRA™ XR proposed) <b>Established/Proper Name:</b> Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir <b>Dosage Form:</b> Film-Coated Tablets <b>Strengths:</b> Single tablet contains: 200 mg dasabuvir, 8.33 mg ombitasvir, 50 mg paritaprevir and 33.33 mg ritonavir		
<b>Applicant:</b> AbbVie, Inc. <b>Agent for Applicant (if applicable):</b> N/A		
<b>Date of Application:</b> September 28, 2015 <b>Date of Receipt:</b> September 28, 2015 <b>Date clock started after UN:</b> N/A		
PDUFA/BsUFA Goal Date: July 28, 2016		Action Goal Date (if different): N/A
Filing Date: November 27, 2015		Date of Filing Meeting: November 3, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s):  <b>Proposed Indication:</b> Treatment of genotype 1 (G1), hepatitis C virus (HCV) infection, in adults, including those with compensated cirrhosis, with or without ribavirin.  <b>Proposed Change:</b> With this original NDA submission the applicant proposes a new formulation of a previously approved product, Viekira Pak™, which was approved under NDA 206619 on December 19, 2014. The applicant proposes a new FDC tablet formulation with the four active substances in Viekira Pak™ into a single dosage form, the “3QD” tablet (dasabuvir 200 mg/ombitasvir 8.33 mg/ paritaprevir 50 mg/ ritonavir 33.33 mg) to enable a once daily (QD) dosing regimen (3 tablets) for the direct acting antivirals (DAAs), and intends to replace Viekira Pak™ after NDA approval. In addition, the applicant is proposing to update the label in accordance with PLLR.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: <b>N/A</b>	<input checked="" type="checkbox"/> 505(b)(1) <b>Original NDA</b> <input type="checkbox"/> 505(b)(2)
<b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <b>N/A not a supplement</b>

Type of BLA	<input type="checkbox"/> 351(a) <b>N/A not a BLA</b> <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	

Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• 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)</li> <li>• The product is a Qualified Infectious Disease Product (QIDP)</li> <li>• A Tropical Disease Priority Review Voucher was submitted</li> <li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>	

Resubmission after withdrawal? <b>No</b>	Resubmission after refuse to file? <b>No</b>
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Part 3 Combination Product? <input type="checkbox"/> <b>N/A – not a Part 3 Combo. Product</b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other: <b>New formulation of approved product called Viekira Pak to new FDC single tablet formulation</b>	<input type="checkbox"/> PMC response: <b>No</b> <input type="checkbox"/> PMR response: <b>No</b> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): <b>N/A – not OTC product</b>
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List referenced IND Number(s): <b>122839</b>
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Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Review is Standard
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>			N/A	
<b>If affected by AIP, has OC been notified of the submission?</b> <b>If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>	N/A	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):  <input checked="" type="checkbox"/> Paid - received September 4, 2015 <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
  <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			

<p><b><u>User Fee Bundling Policy</u></b></p> <p><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i>  <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a></p>		<p>Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i></p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
<p>Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). <b>If yes</b>, answer the bulleted questions below:</p>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		Application not a 505(b)(2)																
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>	N/A																	
<ul style="list-style-type: none"> <li>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)].</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>	N/A																	
<ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><i>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.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>	N/A																	
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>		<input type="checkbox"/>	<input type="checkbox"/>	N/A																	
<p><b>If yes</b>, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<p><i>If there is unexpired, 5-year exclusivity remaining on 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 will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																					
<p><b>Exclusivity</b></p>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		Viekira Pak was given orphan designation status on 7/16/2015 for treatment of peds																

				with HCV (0-16 years of age). Viekira Pak is not yet approved for orphan indication. <a href="#">This orphan designation is not relevant to the current application as indication proposed is for adults only (see below for additional information)</a>
<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see <b>21 CFR 316.3(b)(13)</b>]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Note regarding submission properties: On the FDA Form 356h included with this new NDA submission, this applicant has carried over reference to a pediatric Orphan Drug Designation granted on July 16, 2015 for Viekira Pak (under NDA 206619). As stated above, this designation does not apply to this application at this time (adult only indication at this time). Orphan status will not be referenced in tracking system (DARRTs). Further, the RPM will seek clarification from OOP if designation is accurately carried over as the new NDA is proposing a new formulation of the drug product and superiority to old drug (Viekira Pak) has not been established.
<p><b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p><b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A

considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: 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.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<b>N/A – not a BLA</b>

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?	N/A			
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Applicant has prepared a <i>Multidisciplinary Notes to Reviewer</i> to facilitate the review of this application.
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:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no</b> , explain.				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not a BLA
<b>If yes</b> , BLA #				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, 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.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Provided as separate attachment
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not a paper submission.
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No abuse potential
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>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</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		-New FDC tablet -Peds. waiver request for age < 3y/o. -Request for peds deferral 3 to < 18 y/o

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

<i>approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	iPSP submitted to IND 122839 – approved September 16, 2015. Included in this application
<b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Studies are not required to be completed at the time of this application
<b><u>BPCA:</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary name review was not submitted with the original application, but submitted following request on 26Oct2015.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) : 3QD Regimen Label Comprehensive report			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submission includes PLLR Support document
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>	N/A	Not OTC Product

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

5

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

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Biopharmaceuticals Inspection Consult sent 11/5/2015
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b> 4/14/2015  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		4/14//2015 is the date of preliminary comments from DAVP, as these were accepted by applicant in lieu of meeting. The applicant withdrew meeting request.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 7/13/2015  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		7/13/2015 references date of preliminary comments from DAVP, and these were accepted by applicant in lieu of meeting.
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** November 3, 2015

**BACKGROUND:** Abbvie, Inc., the applicant, has submitted a new NDA (non-NME) proposing a new formulation of a previously approved product, Viekira Pak™, which was approved under NDA 206619 on December 19, 2014.

The applicant proposes a new FDC formulation to include the four active substances in Viekira Pak™ as a single dosage form, the “3QD” tablet (dasabuvir 200 mg/ombitasvir 8.33 mg/ paritaprevir 50 mg/ ritonavir 33.33 mg) to enable a once daily (QD) dosing regimen (3 tablets) for the direct acting antivirals (DAAs), and intends to replace Viekira Pak™ after NDA approval.

The applicant has utilized the approved Viekira Pak label as baseline and modified information to represent this new application. The applicant has included updates according to PLLR and is also proposing format changes and modifications to the Medication Guide.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Suzanne Strayhorn	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Islam Younis		Y
Division Director/Deputy	Debra Birnkrant		Y
	Jeffrey Murray		Y
Office Director/Deputy	Not applicable		N
Clinical	Reviewer:	Tanvir Bell	Y
	TL:	Russell Fleischer	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	Not applicable	N
	TL:	Not applicable	N
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	Not applicable	N
	TL:	Not applicable	N
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Pat Harrington	Y
	TL:	Julian O’Rear	Y

Clinical Pharmacology	Reviewer:	Vikram Arya	Y
	TL:	Islam Younis	Y
• Genomics	Reviewer:	Not Applicable	N
Pharmacometrics	Reviewer:	Luning (Ada) Zhuang	N
	TL:	Jeffrey Florian	Y
Biostatistics	Reviewer:	Not Applicable	N
	TL:	Not Applicable	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	Not Applicable	N
	TL:	Not Applicable	N
Product Quality (CMC) Review Team:	ATL:	Stephen Miller	Y
	RBPM:	Bamidele Aisida	Y
• Drug Substance	Reviewer:	Shrikant Pagay	Y
• Drug Product	Reviewer:	Shrikant Pagay	
• Process	Reviewer:	Christine Falabella	Y
• Microbiology	Reviewer:	Not Applicable	N
• Facility	Reviewer:	Frank Wackes	N
• Biopharmaceutics	Reviewer:	Jing Li	Y
• Immunogenicity	Reviewer:	Not Applicable	N
• Labeling (BLAs only)	Reviewer:	Not Applicable	N
• Other (e.g., Branch Chiefs, EA Reviewer)			N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	TBD	N
	TL:	TBD	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Kemi Asante	N
	TL:		N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Monica Calderon	Y
	TL:	Vicky Borders -Hemphill	N
OSE/DRISK (REMS)	Reviewer:	TBD	N
	TL:	TBD	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	TBD	N
	TL:	TBD	N

Bioresearch Monitoring (OSI)	Reviewer:	TBD	N
	TL:	TBD	N
Controlled Substance Staff (CSS)	Reviewer:	Not Applicable	N
	TL:	Not Applicable	N
Other reviewers/disciplines			
<ul style="list-style-type: none"> <li>• <b>Discipline</b></li> </ul> <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		N
	TL:		N
Other attendees	Danyal Chaudhry (OSE RPM)		Y

**FILING MEETING DISCUSSION:**

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

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain: Application is supported by BA/BE data not investigational site data.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Inspections requested (n=2)</p> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>New Molecular Entity (NDAs only)</u></b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b> Manufacturing Facility in Ireland, planned for inspection, likely February 2016</p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input checked="" type="checkbox"/> N/A  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	None
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES Single site <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Jeffrey Murray	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 2/25/2016 for internal mid-cycle mtg. (NON-NME)	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTION ITEMS</b>	
<input type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE K STRAYHORN  
11/30/2015

ELIZABETH G THOMPSON  
12/01/2015



Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Memorandum of NDA - Initiated in Vivo Bioequivalence Inspection Assignment**

**Date:** November 24, 2015

**From:** Charles R. Bonapace, Pharm.D.  
Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**To:** [ORALOSBIMO@fda.hhs.gov](mailto:ORALOSBIMO@fda.hhs.gov)

**Subject:** Premarket Original Surveillance BIMO Inspection Assignment

**Preannouncement:** No

**Compliance Program:** 7348.001  
**PAC Code:** NON-RESPONSIVE  
**Priority:** High  
**Operation Code:** 12 (Domestic Inspection)  
31 (Domestic Sample Collection)

**Application Number #1:** NON-RESPONSIVE  
**Product Name:**  
**Sponsor:**

**Application Number #2:** NDA 208624  
**Product Name:** Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir  
**Sponsor:** AbbVie  
1 North Waukegan Road  
North Chicago, IL 60064  
TEL: (847) 938-9250  
FAX: (847) 775-4986

Protocol Number:

Application Number	Study Protocol Number
NON-RESPONSIVE	
NDA 208624	M14-566

Inspection Due Date: December 15, 2015

NON-RESPONSIVE

**NDA 208624**

**Study Number #2:** M14-566

**Study Title:** "A Comparison of the Bioavailability of Dasabuvir, Ombitasvir, ABT-450 and Ritonavir Combination Regimen Bilayer Tablets (Film-Coated Quad ER-12: Dasabuvir/Ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) and the Phase 3 Clinical Reference Regimen

(Ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD + Dasabuvir 250 mg BID) in Healthy Subjects.”

**Investigator:** (b)(4)

**# of Subjects:** 154

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Please refer to Table 1 for an example. Please do spot checks to verify that the lot number listed in the table match the reserve samples in the clinical site storage.

**Table 1**

SL NO.	Study number	Drug Name	Fast/Fed	Sponsor	Submission	Study Conduct Dates	Reserve Samples	Quantity	Lot# for Test and Reference
1	XXXXX	Aspirin + Dipyridamole Capsules	Fast	XXXX	USFDA	Dec 24-Dec 31, 2014	At Site	300 for test, 200 for reference	XXXX and XXX
2	XXXXX	Montelukast	Fed	XXXXX	unknown	XXXXX	Third Party	two kits	XXXX and XXX
3	XXXXX	XXXXXXXX	Fast	XXXXXX	Pilot	XXXXX	Not retained	two bottle for test, two bottles for reference	XXXX and XXX

**SECTION A - RESERVE SAMPLES**

Because Study **NON-RESPONSIVE** and Study M14-566 are bioavailability studies and not bioequivalence studies, there is no regulatory requirement for retention of reserve samples. However, CDER review division has requested collection of reserve samples for Study **NON-RESPONSIVE**

**During the clinical site inspection, please:**

- Verify that the site retained reserve samples. Because there is no regulatory requirement, Form FDA 483 should not be issued if the site did not retain reserve samples for study (b)(4) and Study M14-566.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve

samples are representative of those used in the specific studies, and that samples were stored under conditions specified in accompanying records.

- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
645 S. Newstead Ave  
St. Louis, MO 63110  
TEL: 1-314-539-2135

#### **SECTION B - CLINICAL DATA AUDIT**

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

#### **Data Audit Checklist:**

- Confirm that informed consent was obtained for all subjects enrolled in (b)(4) and 50 randomly selected subjects from **Study M14-566**.
- Audit the study records for all subjects enrolled in **Study** (b)(4) and at least 50 randomly selected subjects enrolled in **Study M14-566**.
- Compare the study report submitted to FDA with the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
  - o Number of subject records reviewed during the inspection:\_\_\_\_\_
  - o Number of subjects screened at the site:\_\_\_\_\_
  - o Number of subjects enrolled at the site:\_\_\_\_\_
  - o Number of subjects completing the study:\_\_\_\_\_

- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

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**Additional instructions to the ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to the inspection. Therefore, we request that the OSIS POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

**If you issue Form FDA 483, please forward a copy to the OSIS POC (see below). If it appears that the observations may warrant an OAI classification, notify the OSIS POC as soon as possible.**

**Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the OSIS POC.**

**OSIS POC:** Yiyue Zhang, Ph.D.  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

Tel: (240) 402-6559  
Fax: (301) 847-8748  
E-mail: [yyiyue.zhang@fda.hhs.gov](mailto:yyiyue.zhang@fda.hhs.gov)

**The endorsed EIR and Form 483 documents should be sent to the following:**

If electronic: [CDER-OSIS-BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov)

If paper: Ms. Dinah Miller  
FDA/CDER/OTS/OSIS  
WO51 RM5333 HFD-45  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002

Email cc:  
ORA/PA-FO/LOS-DO/LOS-DIB/Maxwell  
OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Kadavil/Miller  
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang  
OSIS/DGDBE/Haidar/Skelly/Choi

Draft: YZ 11/19/2015  
Edit: CB 11/24/2015  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
(b)(4)

(b)(4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YIYUE ZHANG  
11/24/2015

CHARLES R BONAPACE  
11/24/2015