

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202123Orig1s000**

**OTHER REVIEW(S)**

## Division of Antiviral Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 202123

**Name of Drug:** Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) 200/25/300 mg Fixed Dose Combination Tablets

**Applicant:** Gilead Sciences, Inc.

#### Labeling Reviewed

**Submission Date:** August 4, 2011

**Receipt Date:** August 4, 2011

#### Background and Summary Description:

On November 23, 2011, Gilead Sciences, Inc. (Gilead) submitted a New Drug Application (NDA) for emtricitabine/rilpivirine/tenofovir disoproxil fumarate) 200/25/300 mg fixed dose combination tablets under NDA 202123.

Labeling negotiations began July 18, 2011 with the Sponsor.

The Division sent labeling comments to Gilead on July 18, 2011, July 21, 2011, July 27, 2011, and August 2, 2011.

The Sponsor submitted amendments to this application containing draft labeling on July 25, 2011 and August 4, 2011.

Additionally, a labeling teleconference was held with Gilead on July 22, 2011.

The user fee goal date for this NDA is August 10, 2011.

#### Review

Based on all the labeling comments sent to the Sponsor, there were no significant differences between FDA's current working version of the label and the Sponsor's labeling submitted August 4, 2011.

#### Recommendations

The submitted labeling is acceptable based on labeling negotiations with the Sponsor and should be included in the action letter as the approved labeling.

Linda C. Onaga, MPH  
Regulatory Project Manager

August 5, 2011  
Date

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Karen Winestock  
Chief, Project Management Staff

August 5, 2011  
Date

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/s/  
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LINDA C ONAGA  
08/05/2011

KAREN D WINESTOCK  
08/05/2011

## 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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PMR/PMC Description: Collect dissolution profile data from all full-scale batches manufactured during the first year after approval date

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PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: 8/31/2012  
Final Report Submission: 11/30/2012  
Other: \_\_\_\_\_

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

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

The objective is to provide additional dissolution data from full-scale batches that are needed for the setting of the final regulatory dissolution specifications.

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.”

Collect dissolution profile data from all full-scale batches manufactured during the first year after approval date. The collection of the dissolution data will target the dissolution specifications recommended by the FDA and will include dissolution testing at Stage 1, 2, or 3 as appropriate. Submit the final dissolution report with complete dissolution information/data, a proposal for final dissolution specifications, and data analysis with the number/percentage of batches tested at Stage 1, 2, or 3 or which failed the dissolution specifications recommended by FDA.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

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

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

Collection of dissolution profile data from all full-scale batches manufactured during the first year after approval date. The collection of the dissolution data will target the dissolution specifications recommended by the FDA and will include dissolution testing at Stage 1, 2, or 3 as appropriate.

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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

Collect dissolution profile data from all full-scale batches manufactured during the first year after approval date. The collection of the dissolution data will target the dissolution specifications recommended by the FDA and will include dissolution testing at Stage 1, 2, or 3 as appropriate. Submit the final dissolution report with complete dissolution information/data, a proposal for final dissolution specifications, and data analysis with the number/percentage of batches tested at Stage 1, 2, or 3 or which failed the dissolution specifications recommended by FDA.

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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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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(signature line for BLAs)

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/s/  
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LINDA C ONAGA  
08/03/2011

KENDALL A MARCUS  
08/03/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**PATIENT LABELING REVIEW**

Date: July 15, 2011

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Barbara Fuller, RN, MSN, CWOCN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Risk Management**

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

Drug Name (established name): TRADENAME (emtricitabine, rilpivirine and tenofovir disoproxil fumarate) Tablets

Application Type/Number: NDA 202123

Applicant: Gilead Sciences, Inc

OSE RCM #: 2011-987

## 1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (emtricitabine, rilpivirine and tenofovir disoproxil fumarate) Tablets. The Applicant submitted New Drug Application (NDA) 202123 on September 3, 2011 for a fixed-dose combination tablet of emtricitabine, rilpivirine, and tenofovir disoproxil fumarate for the treatment of HIV-1 infection in treatment-naïve adults.

This product was granted Fast Track designation on October 21, 2009 and was submitted as a Rolling NDA. The final submission for this NDA was submitted on November 23, 2010.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (emtricitabine, rilpivirine and tenofovir disoproxil fumarate) Tablets Patient Package Insert (PPI) received on November 23, 2010, and revised by the review division throughout the review cycle, and sent to DRISK on July 1, 2011
- Draft TRADENAME (emtricitabine, rilpivirine and tenofovir disoproxil fumarate) prescribing information (PI) received November 23, 2010, revised by the review division throughout the current review cycle, and received by DRISK on July 1, 2011
- Approved Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) tablets comparator labeling dated August 6, 2010

## 2 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 3 CONCLUSIONS

The PPI is acceptable with our recommended changes.

## 4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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LATONIA M FORD  
07/15/2011

LASHAWN M GRIFFITHS  
07/15/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

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

**Memorandum**

**Date:** July 6, 2011

**To:** Linda Onaga, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Jessica Fox, PharmD, Regulatory Review Officer  
Sheila Ryan, PharmD, Group Leader  
Michelle Safarik, PA-C, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** NDA 202123 – Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets

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As requested in DAVP's consult request dated March 11, 2011, DDMAC has reviewed the draft labeling (package insert [PI], patient package insert [PPI], carton and container labels) for Complera tablets. DDMAC's comments are based on the proposed substantially complete version of the PI sent to DDMAC on June 30, 2011, and the proposed PPI and carton and container labels sent to DDMAC via email by DAVP on June 27, 2011.

DDMAC's comments on the PI and PPI are provided directly in the attached copy of the labeling. DDMAC has no comments on the carton and container labels.

If you have any questions about DDMAC's comments on the PI, please contact Jessica Fox at 6-5329 or at [Jessica.Fox@fda.hhs.gov](mailto:Jessica.Fox@fda.hhs.gov). If you have any questions about DDMAC's comments on the PPI, please contact Michelle Safarik at 6-0620 or at [Michelle.Safarik@fda.hhs.gov](mailto:Michelle.Safarik@fda.hhs.gov).

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/s/  
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JESSICA M FOX  
07/06/2011

MICHELLE L SAFARIK  
07/06/2011

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
**Office of Medication Error Prevention and Risk Management**

Date:	June 29, 2011
Application Type/Number:	NDA 202123
To:	Debra Birnkrant, MD, Director Division of Antiviral Products
Through:	Kellie Taylor, Pharm.D., MPH, Associate Director Division of Medication Error Prevention and Analysis
From:	Irene Z. Chan, PharmD, BCPS, Team Leader
Subject:	Label and Labeling Memorandum
Drug Name(s):	Complera (Emtricitabine, Rilpivirine, Tenofovir Disoproxil Fumarate) Tablets 200 mg/25 mg/300 mg
Applicant/sponsor:	Gilead Sciences, Inc.
OSE RCM #:	2010-2478

**MEMO TO FILE**

DMEPA evaluated the revised container labels and carton labeling received on June 27, 2011, for Gilead's Complera Tablets in response to a request from the Division of Antiviral Products (see Appendices A and B). DMEPA finds the revised container labels and carton labeling acceptable. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this memorandum. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Brantley Dorch, at 301-796-0150.

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/s/  
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IRENE Z CHAN  
06/29/2011

KELLIE A TAYLOR  
06/29/2011

**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: June 28, 2011

TO: Debra B. Birnkrant, MD  
Director  
Division of Antiviral Products (DAVP)

John Lazor, Pharm.D.  
Director  
Division of Clinical Pharmacology 4 (DCP4)

FROM: Gopa Biswas, Ph.D.  
Jang Ik Lee, Ph.D.  
Martin K. Yau, Ph.D.  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

THROUGH: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 202-123 Emtricitabine 200 mg/Rilpivirine 25 mg/Tenofovir Disoproxil Fumarate 300 mg Tablet sponsored by Gilead Sciences, Inc.

At the request of DAVP and DCP4, DBGC conducted inspections of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** GS-US-264-0103

**Study Title:** "Bioequivalence Study of Two, Fixed-dose, Combination Tablet Formulations Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the Concurrent Administration of the Individual Components"

The inspection of clinical portion of the study was conducted at SeaView Research Inc., Miami, FL from May 16-19, 2011.

Inspections of analytical portions were conducted at (b)(4)  
(b)(4) (for Rilpivirine) (b)(4) and (b)(4)  
(b)(4) (for Emtricitabine and Tenofovir) (b)(4)

(b)(4) There were no significant findings following the inspections at SeaView Research and (b)(4) and no form FDA-483 was issued to these two sites. Following the inspection at (b)(4) (b)(4) Form FDA-483 was issued (Attachment 1). An electronic response to inspectional findings was received from (b)(4) on May 11, 2011 followed by the hard copy on May 23, 2011 (Attachment 2). Our evaluation of objectionable items and response from (b)(4) International follows:

**Analytical site: (b)(4) (Rilpivirine):**

**1. Failed to use freshly prepared calibrators in the validation of processed sample and autosampler stability.**

All calibration standards for stability comparisons had been frozen and stored for at least five days before use in these experiments. In response to the observation, (b)(4) conducted additional validation experiments using freshly-prepared calibration standards and demonstrated processed sample and autosampler stability for 143 hrs. The results are adequate and acceptable.

**2. Failed to demonstrate the long term stability of TMC278 (Rilpivirine) in human plasma in presence of Emtricitabine and Tenofovir for the duration of sample storage (51 days) at -20°C.**

Long term stability for RPV in presence of Tenofovir and Emtricitabine was only demonstrated for 39 days by (b)(4). In their response, (b)(4) acknowledged the observation and provided data for long term stability at -20°C and -70°C for 125 days. The data is acceptable and adequate to cover the total period of sample storage.

**3. Failed to document the movement of samples in freezer log for -20 degrees C walk-in freezer (b)(4) for 3 cycles in the freeze thaw stability experiment.**

(b)(4) assessed Rilpivirine stability in presence of Emtricitabine and Tenofovir for 3 freeze thaw cycles at -20°C and -70°C. The time of removal and return of the stability samples from the storage freezers was not documented in the freezer log books. However, the freezer numbers and the time of sample movement from freezers were documented in the sample processing sheets. (b)(4) concurred with the observation and stated in their response that the relevant SOP and freezer log template has been revised

to document these freezing and thawing details for future studies.

**4. Protection from light was not documented in the lab notebook during weighing of TMC278 (Rilpivirine) or during sample processing. Specifically, Rilpivirine was found to be unstable under white light conditions during validation study FK4169.**

In their response, (b)(4) acknowledged the observation and stated that the study samples were processed under yellow light according to assay instructions but failed to document in the laboratory notebook. (b)(4) explains that exposure to light would have caused an increase in (b)(4) of Rilpivirine in study samples. The (b)(4) was monitored during the study by including "resolution sample" containing a mix of Ripivirine and (b)(4) beginning and end of each analytical run. The detectable level of (b)(4) remained less than (b)(4) of Rilpivirine in the study samples and therefore the samples were protected from light. DSI agrees with the explanation.

Please note that (b)(4) conducted validation of Ripivirine stability in presence of 200 ng/ml of Tenofovir and 500 ng/ml of Emtricitabine. These concentrations do not represent the maximum concentration for the two analyte in study samples. However, the review division has requested additional data for Ripivirine stability in presence of higher concentration of Tenofovir and Emtricitabine (600 ng/ml and 2400 ng/ml respectively). Data is awaited from (b)(4)

**5. Audit trails for validation study FK4169 were not available for review. Assays for stock solution stability and stability under light conditions were conducted under this study.**

Audit trails for (b)(4) method validation study were not available for review during the inspection. According to the firm, at the time of study the firm generated electronic copies of audit trails to file as "business copies" and did not archive them with source records. The paper copies of audit trails were not generated for the study. Firm stated that the electronic copies of audit trails could not be retrieved any more. In response to the observation, (b)(4) provided copies of "Chemstation version A06.03" software audit trail obtained from (b)(4) but it does not contain detailed information on changes made to the integration parameters during the study.

However, (b)(4) submitted additional data to demonstrate stock solution stability protected from light at room temperature and -20°C for 25 days and 117 days respectively. The results are acceptable upon review.

**Conclusion:**

Following evaluation of the inspectional findings at SeaView Research, Inc. (clinical study site), (b)(4) (analytical site for Emtricitabine and Tenofovir) and (b)(4) (analytical site for Rilpivirine) as well as the 483 response submitted by (b)(4), DBGC recommends the following:

1. The OCP reviewer should review the Rilpivirine stability data generated in the presence of higher concentration of Tenofovir and Emtricitabine (600 ng/ml and 2400 ng/ml respectively), when these addition stability data are submitted by (b)(4) to OCP.
2. The remaining clinical and bioanalytical data from Study GS-US-264-0103 are acceptable for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Gopa Biswas Ph.D.

Jang Ik Lee, Ph.D.

Martin K. Yau, Ph.D.

**Final Classifications:**

NAI-SeaView Research Inc., Miami, FL

VAI- (b)(4)

NAI- (b)(4)

Page 5 -NDA 202-123, Emtricitabine 200 mg/Rilpivirine 25 mg/  
Tenofovir Disoproxil Fumarate 300 mg Tablet

cc:

DSI/Ball/Salewski/Viswanathan/Haidar/Yau/Biswas/Lee/Dejernett/CF  
OTS/OCP/DCP4/Lazor

OND/OAP/DAVP/Birnkrant

HFD-530/Linda Onaga (Division of Antiviral Products)

HFR-SE250/Brunilda Torres

HFR-CE750/Olenjack

Draft: GB 5/16/2011

Edit: MKY 6/28/2011

DSI: 6182; O:\BE\eircover\202123gil.emt.ril.ten.doc

FACTS: (b) (4)

EMAIL:

CDER DSI PM TRACK

## **ATTACHMENT 1**

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**ATTACHMENT 2**

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/s/  
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GOPA BISWAS  
06/30/2011

MARTIN K YAU  
06/30/2011

JANG IK LEE  
06/30/2011

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**Application:** NDA 202-123

**Name of Drug:** Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (FTC/RPV/TDF)

**Applicant:** Gilead Sciences

## Labeling Reviewed

**Submission Date:** October 19, 2010

**Receipt Date:** October 19, 2010

## Background and Summary Description

Gilead Sciences, Inc. (Gilead) is developing emtricitabine (FTC), rilpivirine (RPV) and tenofovir disoproxil fumarate (TDF) fixed-dose combination (FDC) tablet for the treatment of HIV-1 infection. On November 23, 2010, Gilead submitted the final piece of the new drug application (NDA) to market the new FDC tablet in the United States. Within the first 60 days of the review cycle, the Division of Antiviral Products (DAVP) held a multi-disciplinary meeting to discuss the application. At this meeting, it was recognized that without the information on the recently identified (b)(4) degradants, there was not sufficient information to approve this NDA. Gilead received a Refusal to File (RTF) letter from the Division on January 20, 2011, which outlined the deficiencies and information need to complete the NDA submission.

Gilead re-submitted the NDA for this FDC tablet on February 10, 2011. Emtricitabine and tenofovir disoproxil fumarate are approved antiretroviral products. Rilpivirine is an investigational product developed by Tibotec, filed on July 23, 2010. Gilead Sciences and Tibotec, Inc are partners in the development of the fixed dose combination product.

The labeling (in SPL format) was submitted electronically to the NDA.

## Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages.

## Recommendations

In addition, the following labeling issues were identified:

1. Please avoid error prone abbreviations, symbols, and dose designations. Please update the label with the following:
  - a. Do not use (b) (4) since it may be mistaken for the number 1. Please update the label with “per” instead of (b) (4). Use 5 mg per 10mL.
  - b. For the text do not use the symbol for less than (b) (4). Please spell the word in the label. The symbols can be used in tables.
2. Highlights Section:
  - a. Use in Specific Population (Page 1),
    - i. Please remove (b) (4) from the Highlights section of the physician insert.
    - ii. Please remove the following (b) (4)
3. Table of Content
  - a. The Highlights and Table of Contents do not fit on one page, please insert the Table of Contents on page 2 of the labeling.
  - b. Section 17 should be listed as, **17 PATIENT COUNSLEING INFORMATION**
4. Full Prescribing Information
  - a. Section 17 should be listed as  
17 PATIENT COUNSELING INFROMATION  
*See FDA-Approved Patient Labeling (Patient Information)*
5. *Patient Information*
  - a. Remove (b) (4)

All labeling issues identified on the following pages with an “X” and identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by May 2, 2011. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

## Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

### Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading - if no contraindications are known, it must state "None")
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)

• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.”
- **Indications and Usage**
  - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
  - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
  - All contraindications listed in the FPI must also be listed in HL.
  - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.
- **Patient Counseling Information Statement**
  - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”
- **Revision Date**
  - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**
  - A horizontal line must separate the TOC and FPI.
  - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
  - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for

the text.

- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“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.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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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LINDA C ONAGA  
05/11/2011

KAREN D WINESTOCK  
05/12/2011

## 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 #202-123 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: TBN Established/Proper Name: Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (FTC/RPV/TDF) Dosage Form: Tablets Strengths: 200 mg FTC/25 mg RPV/ 300 mg TDF		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: February 10, 2011 Date of Receipt: February 10, 2011 Date clock started after UN:		
PDUFA Goal Date: August 10, 2011	Action Goal Date (if different):	
Filing Date: April 11, 2011	Date of Filing Meeting: March 9, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a>                      and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input checked="" type="checkbox"/>	
Part 3 Combination Product? No  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 106,252, IND 53,971; IND 52,849; IND 67,671; IND 67,699				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			Sponsor re-submitted proprietary name request to NDA for review on 2/14/11
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
<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: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			
<b>User Fee Status</b>  <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>	<b>Payment for this application:</b> <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<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>	<b>Payment of other user fees:</b> <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>(NDAs/NDA Efficacy Supplements only)</b>				
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>				
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product have orphan exclusivity for the same		x		

indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements only)  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		x		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s only)?			x	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

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)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2	X			

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

(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"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), 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)?  <i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			Hyperlinks are provided
<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)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with	X			

authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <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>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <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>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	Electronic submission

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	x			Addressed in 11/23 submission, however no dates proposed for submitting PREA studies.

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

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			Gilead only stated trials that will be conducted with the individual drugs. Pending the result of the two components of the FDC, the FDC peds trials will be determined
<b>BPCA (NDAs/NDA efficacy supplements only):</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>		X		
<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>	X			Under review
<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/DCRMS via the DCRMSRMP mailbox</i>		x		
<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 checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (PEPFAR carton and container labels)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			

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

<i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			
<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 PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Yes sent on 3/11/11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Yes sent on 3/11/11
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			DSI consult for BE audit for international site
<i>If yes, specify consult(s) and date(s) sent:</i>				

4

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

<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>	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> June 3, 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** March 9, 2011

**BLA/NDA/Supp #:** 202-123

**PROPRIETARY NAME:**

**ESTABLISHED/PROPER NAME:** Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (FTC/RPV/TDF)

**DOSAGE FORM/STRENGTH:** Tablets 200 mg FTC/25 mg RPV/ 300 mg TDF

**APPLICANT:** Gilead Sciences

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of HIV-1 Infection

**BACKGROUND:** Gilead Sciences, Inc. (Gilead) is developing emtricitabine (FTC), rilpivirine (RPV) and tenofovir disoproxil fumarate (TDF) fixed-dose combination (FDC) tablet for the treatment of HIV-1 infection. On November 23, 2010, Gilead submitted the final piece of the new drug application (NDA) to market the new FDC tablet in the United States. Within the first 60 days of the review cycle, the Division of Antiviral Products (DAVP) held a multi-disciplinary meeting to discuss the application. At this meeting, it was recognized that without the information on the recently identified (b) (4) there was not sufficient information to approve this NDA. Gilead received a Refusal to File (RTF) letter from the Division on January 20, 2011, which outlined the deficiencies and information need to complete the NDA submission.

Gilead re-submitted the NDA for this FDC tablet on February 10, 2011. Emtricitabine and tenofovir disoproxil fumarate are approved antiretroviral products. Rilpivirine is an investigational product developed by Tibotec, filed on July 23, 2010. Gilead Sciences and Tibotec, Inc are partners in the development of the fixed dose combination product.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Linda C. Onaga, MPH	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Sarah Robertson, PharmD		Y
Clinical	Reviewer:	Yodit Belew, MD	Y
	TL:	Kimberly Struble, PharmD	Y

Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Lisa Naeger, PhD	Y
	TL:	Jules O'Rear, PhD	Y
Clinical Pharmacology	Reviewer:	Stanley Au, PharmD	Y
	TL:	Sarah Robertson, PharmD	Y
Biostatistics	Reviewer:	Fraser Smith, PhD	Y
	TL:	Greg Soon, PhD	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton, PhD	Y
	TL:	Hanan Ghantous, PhD, DABT	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rao Kambhampati, PhD	Y
	TL:	Dorota Mateka, PhD	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	LaToya Toombs	Y

	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Martin Yau, PhD	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
CMC Biopharmaceutical Reviewer	Elsbeth Chikhale		Y
OSE Project Manager	Brantley Dorch		Y
Other Attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <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, explain:</b></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 checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p> <p>Please submit Individual Subject Data Listing (which includes Data Tabulation Dataset in</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>.xpt format) for study GS-US-264-0101.</p> <p>Please revise the ‘Pediatric Study Deferral Request’ to include anticipated dates for study protocol submission(s), study(ies) completion and study report(s) submission.</p>	
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain: BE studies used to support application.</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 original NME or BLA application, 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>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></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>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<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 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>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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>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>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> <li><b>If no</b>, was a complete EA submitted?</li> <li><b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<b>Comments:</b>	
<u><b>Facility Inspection</b></u> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Facility/Microbiology Review (BLAs only)</b></u>  <b>Comments:</b>	<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
<u><b>CMC Labeling Review</b></u>  <b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Debra Birnkrant, MD, Division Director  <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 type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u> <input type="checkbox"/> Standard Review

<input checked="" type="checkbox"/>	Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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/s/  
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LINDA C ONAGA  
03/25/2011

# DSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** February 10, 2011

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** (Require for International Inspections)  
John Lazor, Pharm.D.  
Director, Division of Clinical Pharmacology 4

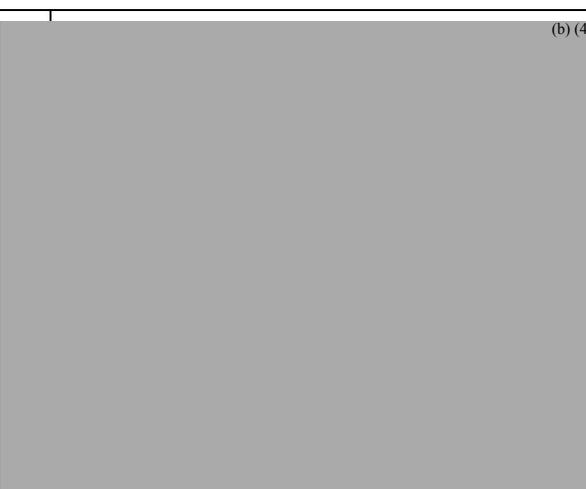
**FROM:** Linda C. Onaga, MPH, Regulatory Project Manager, Division of Antiviral Products,  
HFD - 530

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 202-123  
Emtricitabine 200 mg/Rilpivirine 25 mg/Tenofovir Disoproxil Fumarate 300mg Tablet  
Gilead Sciences, Inc.

### Study/Site Identification:

The following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
GS-US-264-103: Bioequivalence Study of Two, Fixed-dose, Combination Tablet Formulations Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the	Audrey E. Martinez MD SeaView Research, Inc. 3898 NW 7th Street Miami, FL 33126 Telephone: (305)-644-9903 Fax: (305)-643-2818	Two bioanalytical laboratories were used to measure the three analytes:  1) <u>Emtricitabine and tenofovir</u>  (b) (4)  2) <u>Rilpivirine</u>

Concurrent Administration of the Individual Components		 (b) (4)
--	--	--

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

X Other (please explain):

The data from the GS-US-264-103 trial provides critical information in evaluating the bioequivalence of the emtricitabine, rilpivirine, and tenofovir analytes when administered as the to be marketed fixed dose combination tablet compared to the three analytes coadministered as individual formulations under fed conditions. Specifically, for the rilpivirine analyte, the trial provides comparative exposure data for the fixed dose combination tablet versus the Phase 3/to be marketed rilpivirine formulation currently under NDA review.

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **June 10, 2011**. We intend to issue an action letter on this application by **August 10, 2011**.

Should you require any additional information, please contact Linda Onaga (301-796-0759).

Concurrence: Debra Birnkrant, MD, Director, DAVP  
Name Medical Team Leader: Kim Struble  
Medical Reviewer: Yodit Belew  
Clinical Pharmacology Team Leader: Sarah Robertson  
Clinical Pharmacology Reviewer: Stanley Au

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/s/  
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LINDA C ONAGA  
02/11/2011

JOHN A LAZOR  
02/11/2011



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

Date: February 2, 2011

To: Debra Birnkrant, MD, Director  
Division of Antiviral Products

Through: Irene Z. Chan, PharmD, BCPS, Acting Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis  
(DMEPA)

From: L. Sheneé Toombs, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Complera (Emtricitabine, Rilpivirine Hydrochloride and  
Tenofovir Disoproxil Fumarate) Tablets  
200 mg/27.5 mg/300 mg

Application Type/Number: NDA 202123

Applicant: Gilead Sciences, Inc.

OSE RCM #: 2010-2478

# CONTENTS

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3	RECOMMENDATIONS .....	3
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## 1 INTRODUCTION

This review evaluates the proposed labels and labeling for Complera from a medication error perspective.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)<sup>1</sup>, principals of human factors, and lessons learned from postmarketing experience in our evaluation of labels and labeling of drug products. This review evaluates the labels and labeling submitted on September 3, 2010 (see Appendices A through B) and the insert labeling submitted October 19, 2010 (no image).

## 3 RECOMMENDATIONS

Our evaluation of the container labels and carton labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 Comments to the Division. We request the recommendations for the container labels and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Brantley Dorch, at 301-796-0150.

### 3.1 COMMENTS TO THE DIVISION

#### A. GENERAL COMMENT

1. DMEPA notes the use of the abbreviation (b) (4) throughout the insert labeling. Replace the abbreviation with the intended meaning of the abbreviation (b) (4) to avoid confusion and misinterpretation.
2. The strength presentation is Emtricitabine 200 mg, Rilpivirine 25mg and Tenofovir Disoproxil Fumarate 300 mg; however, a statement on the container label notes, “Each tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine and 300 mg of tenofovir disoproxil fumarate which is equivalent to 245 mg of tenofovir disoproxil. DMEPA is unclear whether the strength for this product is based on the salt or the active moiety. DMEPA defers to CMC for recommendations on the strength presentation.

#### B. HIGHLIGHTS OF PRESCRIBING INFORMATION-DOSAGE FORMS AND STRENGTHS

The Dosage Forms and Strength statement does not clearly convey the milligram content of each ingredient contained in each tablet. Revise the statement to read, “Tablet containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 300 mg of tenofovir disoproxil fumarate”.

---

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

### C. FDA-APPROVED PATIENT LABELING

The Applicant utilizes upper-case letters for proprietary names of drugs they market (i.e. EMTRIVA, VIREAD, TRUVADA, ATRIPLA, HEPSERA) throughout the Patient Package Insert. DMEPA recommends modifying the tradenames to appear in title case (i.e, Emtriva) to improve readability. Words set in title case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all upper case.

### 3.2 COMMENTS TO THE APPLICANT

#### A. General Comments for Container Label (30 count) and Carton Labeling (1 x 30 count)

1. We note the placeholder, “Tradename” is being used as a substitute for the proprietary name. Once the proprietary name is approved, ensure that the established name is at least ½ the size of the proprietary name and ensure the established name has a prominence commensurate with the prominence with which the proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. Revise the presentation of the established name so that the strength of each ingredient appears below the established name and not within. Revise to read as follows:  
TRADENAME  
(Emtricitabine, Rilpivirine, Tenofovir Disoproxil Fumarate) Tablets  
200 mg/25 mg/300 mg
3. Relocate the net quantity, 30 tablets, to the upper right corner of the principal display panel so that it is away from the product strength.
4. Relocate the statement, “Gilead Access Program” to the side panel. The principal display panel should be reserved for pertinent information. Additionally, this statement crowds the principal display panel.

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/  
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LATOYA S TOOMBS  
02/02/2011

IRENE Z CHAN  
02/02/2011

CAROL A HOLQUIST  
02/02/2011

## 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 #202-123 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: TBN Established/Proper Name: Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (FTC/RPV/TDF) Dosage Form: Tablets Strengths: 200 mg FTC/25 mg RPV/ 300 mg TDF		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: November 22, 2010 Date of Receipt: November 23, 2010 Date clock started after UN:		
PDUFA Goal Date: May 23,2011	Action Goal Date (if different):	
Filing Date: January 22, 2011	Date of Filing Meeting: January 7, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1, 4		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</b></i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a> <i><b>and refer to Appendix A for further information.</b></i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? No  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): IND 106,252, IND 53,971; IND 52,849; IND 67,671; IND 67,699				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			Sponsor submitted proprietary name request to NDA for review Due Date 2/8/2011
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
<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: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			
<b>User Fee Status</b>  <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>	<b>Payment for this application:</b>  <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<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>	<b>Payment of other user fees:</b>  <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>(NDAs/NDA Efficacy Supplements only)</b>				
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>				
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product have orphan exclusivity for the same		x		

indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>				
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<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		x		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>			x	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

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

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, <b>both</b> the applicant and the 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?	X			Hyperlinks are provided
<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)?	X			
<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)?	X			
<i>Forms must be signed by the <b>APPLICANT</b>, 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?	X			
<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>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic 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>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>PREA</b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	x			Addressed in 11/23 submission, however no dates proposed for submitting PREA studies.
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		

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

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	x			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)  <i>If no, request in 74-day letter</i>	X			Gilead only stated trials that will be conducted with the individual drugs. Pending the result of the two components of the FDC, the FDC peds trials will be determined
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</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>		X		
<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>	X			Under review
<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/ DCRMS via the DCRMSRMP mailbox</i>		x		
<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 checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (PEPFAR carton and container labels)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

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

<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 PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?				Pending
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				Pending
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			DSI consult for BE audit for international site
<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>		X		

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> June 3 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 1/7/2011

**BLA/NDA/Supp #:** 202-123

**PROPRIETARY NAME:**

**ESTABLISHED/PROPER NAME:** Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (FTC/RPV/TDF)

**DOSAGE FORM/STRENGTH:** Tablets 200 mg FTC/25 mg RPV/ 300 mg TDF

**APPLICANT:** Gilead Sciences

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of HIV-1 Infection

**BACKGROUND:** Gilead Sciences submitted a rolling 505(B)(1) New Drug application for a fixed dose combination tablet of emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate (FTC/RPV/TDF) for the treatment of HIV-1 infection in adults. Emtricitabine and tenofovir disoproxil fumarate are approved antiretroviral products. Rilpivirine is an investigational product developed by Tibotec which has been filed on July 23, 2010. Gilead Sciences and Tibotec, Inc are partners in the development of the fixed dose combination product.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Linda C. Onaga, MPH	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Sarah Robertson, PharmD		Y
Clinical	Reviewer:	Yodit Belew, MD	Y
	TL:	Kimberly Struble, PharmD	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Lisa Naeger, PhD	Y
	TL:	Jules O'Rear, PhD	Y
Clinical Pharmacology	Reviewer:	Stanley Au, PharmD	Y
	TL:	Sarah Robertson, PharmD	Y
Biostatistics	Reviewer:	Fraser Smith, PhD	Y
	TL:	Greg Soon, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton, PhD	Y
	TL:	Hanan Ghantous, PhD, DABT	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rao Kambhampati, PhD	Y
	TL:	Dorota Mateka, PhD Steven Miller, PhD	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Martin Yau, PhD	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	LaToya Toombs	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
CMC Biopharmaceutical Reviewer	Elsbeth Chikhale		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <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, explain:</b></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 checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p> <p>Please submit Individual Subject Data Listing (which includes Data Tabulation Dataset in .xpt format) for study GS-US-264-0101.</p> <p>Please revise the (b) (4) to include anticipated dates for study protocol submission(s), study(ies) completion and study report(s) submission.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> BE studies used to support</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

application.	
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, 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>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIostatISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> Issues remain regarding a secondary degradation product, called (b)(4) related to the emtricitabine drug substance. The sponsor must provide confirmatory evidence describing levels of (b)(4) in test article from the previous qualification study titled “A 14-Day Oral Gavage Study Comparing Non-Degraded and Degraded TDF/FTC in Sprague-Dawley Rats”. The evidence should describe (b)(4) diastereomer levels present at the time the study was conducted. Absent that confirmatory evidence, an additional qualification study may be required.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> During the meeting, it was recognized that without the information on the recently identified (b)(4) degradants (planned for submission in late February 2011), there was not sufficient information to approve this NDA. For this reason, Refuse-To-File is recommended for NDA 202-123 based on the need for information to establish the safe levels of these two recently recognized emtricitabine degradants (b)(4) and to assure that these impurities are controlled at or below the safe level during storage and use of the drug product. Further information on this issue is contained in Gilead's Dec 23, 2010, Request for Comment (NDAs 202-123, 21-752 and 21-937), Gilead's Nov 11, 2010, background package (e.g., Sequence No. 367 to NDA 21-752) and FDA's meeting minutes for the subsequent Dec 13, 2010, teleconference with Gilead (documented under NDA 21-752 on Dec 23, 2010).</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Linda C. Onaga</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p>	

<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input checked="" type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p> <p>At the multi-disciplinary filing meeting, ONDQA and Pharmacology/Toxicology reviewers concluded that the information in the NDA at the time of filing lacked sufficient information to approve this NDA. Refuse to File was recommended based on the comments from ONDQA and Pharmacology/Toxicology reviewers.</p>
<input type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These

	sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a>
<input type="checkbox"/>	Other

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/s/  
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LINDA C ONAGA  
01/28/2011

# DSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** December 7, 2010

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** (Require for International Inspections)  
John Lazor, Pharm.D.  
Director, Division of Clinical Pharmacology 4

**FROM:** Linda C. Onaga, MPH, Regulatory Project Manager, Division of Antiviral Products,  
HFD - 530

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 202-123  
Emtricitabine 200 mg/Rilpivirine 25 mg/Tenofovir Disoproxil Fumarate 300mg Tablet  
Gilead Sciences, Inc.

### Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
GS-US-264-103: Bioequivalence Study of Two, Fixed-dose, Combination Tablet Formulations Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate	Audrey E. Martinez MD SeaView Research, Inc. 3898 NW 7th Street Miami, FL 33126 Telephone: (305)-644-9903 Fax: (305)-643-2818	Two bioanalytical laboratories were used to measure the three analytes:  1) <u>Emtricitabine and tenofovir</u>  (b) (4)  2) <u>Rilpivirine</u>

Compared to the Concurrent Administration of the Individual Components		(b) (4)
		(b) (4)

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

X Other (please explain):

The data from the GS-US-264-103 trial provides critical information in evaluating the bioequivalence of the emtricitabine, rilpivirine, and tenofovir analytes when administered as the to be marketed fixed dose combination tablet compared to the three analytes coadministered as individual formulations under fed conditions. Specifically, for the rilpivirine analyte, the trial provides comparative exposure data for the fixed dose combination tablet versus the Phase 3/to be marketed rilpivirine formulation currently under NDA review.

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **March 23, 2011**. We intend to issue an action letter on this application by **May 23, 2011**.

Should you require any additional information, please contact Linda Onaga (301-796-0759).

Concurrence: Debra Birnkrant, MD, Director, DAVP  
Name Medical Team Leader: Kim Struble  
Medical Reviewer: Yodit Belew  
Clinical Pharmacology Team Leader: Sarah Robertson  
Clinical Pharmacology Reviewer: Stanley Au

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/s/  
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LINDA C ONAGA  
12/07/2010

JOHN A LAZOR  
12/07/2010