CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208351Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208351
Review 2
Review Date: Feb 3, 2016

Drug Name/Dosage Form	emtricitabine/rilpivirine/tenofovir alafenamide
Strength	200mgFCT/25mgRPV/25mgTAF
Route of Administration	PO
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	01-Jul-2015
Amendment	06-Aug-2015
Amendment	24-Sep-2015
Amendment	16-Oct-2015
Amendment	13-Oct-2015
Amendment	13-Nov-2015
Amendment	30-Nov-2015
Amendment	04-Jan-2016
Amendment	15-Jan-2016

Quality Review Team

Responsibility	Primary Reviewer
RBPM	Florence Aisida
Drug Substance	Haripada Sarker
Drug Product	George Lunn
Drug Process	Steven Frisbee
Biopharmaceutics	Om Anand
Facility	Rose Xu
EA	James Laurenson
ORA Contact	Paul Perdue, Jr.
ATL	Stephen Miller

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS
(b) (4) [redacted]	II	[redacted]	(b) (4) [redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	IV	[redacted]	[redacted]	Adequate
[redacted]	IV	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]		[redacted]	[redacted]	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	123098	IND for this combination during development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical		See separate review		
Environmental Assessment	AC	J.Laurenson provided input to G.Lunn's review	Sept 1, 2015	G.Lunn
Other	NA			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the quality of the drug substances and this drug product, including establishment of a PMC for the rilpivirine dissolution time point. All manufacturing facilities have now been determined to be in acceptable status. From the Product Quality perspective, NDA 208351 is recommended for approval.

Labeling recommendations from the Product Quality perspective have been provided to the OND PM, and were considered during final labeling. All labels and labeling remain acceptable from the Product Quality perspective.

1. Summary of Complete Response issues NA
2. Action letter language, related to critical issues such as expiration date
   We also acknowledge receipt of information related to ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide), 200/25/25 mg fixed-dose combination tablet for your Gilead Access Program that was reviewed as part of this application.
3. Benefit/Risk Considerations
   Evaluation of the quality aspects of Odefsey tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

A PMC has been set up to finalize the timepoint for the rilpivirine dissolution acceptance criterion after batch release data are available (b) (4) of commercial manufacturing experience.

II. Summary of Quality Assessments

A. Drug Substance [Tenofovir Alafenamide Fumarate] Quality Summary

Information Relevant to Impurity Control: Maximum Daily Dose of TAF fumarate is 25 mg/day for patients using this product. Acceptable Intake of Mutagenic Impurities: (b) (4) (b) (4) at 25 mg/day maximum dose = (b) (4) % for TAF fumarate (b) (4) (b) (4) (b) (4)

For additional drug substance information, see NDA 207561 and detailed review notes, below.

A. Drug Substance [Emtricitabine] Quality Summary

See NDA 21752 and detailed review notes, below.

A. Drug Substance [Rilpivirine Hydrochloride] Quality Summary

See NDA 202022, DMF (b) (4), and detailed review notes, below.

B. Drug Product [Emtricitabine, Rilpivirine and Tenofovir Alafenamide Tablets] Quality Summary

1) Strength: 200mg / 25mg / 25mg
2) Description/Commercial Image of US Product: gray capsule-shaped film-coated (b) (4) tablets debossed with "GSI" on one side and "255" on the other. Description/Commercial Image of Access Product: (b) (4) - (b) (4)
3) Summary of Product Design: The product is a (b) (4) tablet with three drug substances, and is produced using (b) (4) processes. The specification includes tests for appearance, identity, (b) (4) assay, degradants, uniformity, dissolution, and microbial limits. The specification is largely (b) (4) for an immediate release solid oral dosage form and a satisfactory justification is provided. After extensive discussion the (b) (4) (b) (4) NMT (b) (4)%. The degradants are toxicologically qualified at the proposed limits. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust. Satisfactory batch analyses are provided for 12 batches of (b) (4).
4) List of Excipients: lactose monohydrate, microcrystalline cellulose, povidone, polysorbate 20, croscarmellose sodium, magnesium stearate, and (b) (4) (b) (4) The magnesium stearate is from (b) (4) (b) (4) and the lactose (b) (4) (b) (4). Gray (b) (4) (b) (4) film coats are used. All excipients and the components of the film coat are compendial.
5) Process Selection (Unit Operations Summary):
   i. (b) (4)
   ii.
   iii.
   iv. Critical equipment: None.

6) Container Closure: The tablets are packaged 30 count in 75 mL white HDPE bottles containing (b) (4) of silica gel desiccant and a polyester coil. The bottles are capped with (b) (4) screw caps and an induction seal.
7) Expiration Date & Storage Condition: The applicant claims a 24 month expiration dating period with the storage statement: "Store below 30°C". This is supported with a statistical analysis of the available stability data, including the 30°C/75% RH long-term data, and is reasonable. The expiration dating period (b) (4) (b) (4)

   Twelve months of satisfactory stability data are provided for one batch and 9 months for 2 batches stored at 25°C/60% RH and 30°C/75% RH as well as 6 months for 3 batches stored at 40°C/75% RH. Lesser amounts of stability data are provided for other batches. There are no out of specification results. The only obvious trends are an increase in TAF impurities (b) (4) (b) (4) (b) (4) There is an (b) (4) (b) (4) (b) (4) (b) (4) Data (b) (4) (b) (4). This is why it is important to (b) (4) to NMT (b) (4) %. There is no obvious trend in dissolution. The stability behavior of the gray (b) (4) tablets appears to be equivalent. The applicant reports a (b) (4) in TAF assay.
8) List of Co-Packaged Components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Odefsey Tablets
Non Proprietary Name of the Drug Product	Emtricitabine, Rilpivirine and Tenofovir Alafenamide Tablets
Non Proprietary Name of the Drug Substance	Emtricitabine; Rilpivirine Hydrochloride; Tenofovir Alafenamide Fumarate
Proposed Indication(s) including Intended Patient Population	Complete regimen for the treatment of HIV-1 infection in (b) (4) patients 12 years of age and older
Duration of Treatment	Chronic (classified as 1-10 years of use for purposes of setting limits on mutagenic impurities per ICH M7)
Maximum Daily Dose	1 tablet per day
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance: An official designation has not been requested, however, the Applicant considers emtricitabine (FTC) to be a BCS Class 1 compound, rilpivirine hydrochloride (RPV) to be a BCS Class 2 compound and tenofovir alafenamide (TAF) to be a BCS Class 3 compound.

- Drug Product: An official designation has not been requested for this combination drug product containing BCS Class 1, 2 and 3 drug substances.

2. Biowaivers/Biostudies:
   - PK studies: **Study GS-US-366-1159** (OCP is reviewing this study)
   - Biowaiver Requests: Not Applicable
   - IVIVC: Not Applicable

3. Dissolution method: **ACCEPTABLE**
   - The following proposed dissolution methods are acceptable:

   For emtricitabine (FTC) and tenofovir alafenamide (TAF):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	500 mL	pH 5.5, 50 mM Sodium Citrate @37.0± 0.5° C	UPLC/UV λ= (b) (4) nm

   For rilpivirine (RPV):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	1000 mL	0.5% Polysorbate 20 in 0.01 N HCl, pH 2 @37.0± 0.5° C	UPLC/UV λ= (b) (4) nm

4. **Dissolution Acceptance Criterion: ACCEPTABLE WITH PMC**

   The revised dissolution acceptance criterion of Q= (b) (4) % at 20 minutes for emtricitabine (FTC) and tenofovir alafenamide (TAF) is acceptable and was agreed with the Applicant during a T-con between FDA and the Applicant on 12/3/15.

   The dissolution acceptance criterion for rilpivirine (RPV) could not be agreed upon. However, the Applicant agreed to an interim rilpivirine dissolution acceptance criterion of Q= (b) (4) % at 45 minutes and also agreed to a Post-Marketing Commitment [PMC] to compare dissolution results from all commercial batches at the 30-minute and 45-minute time points. In addition, the Applicant agreed to provide the requested information as a supplement 18 months post NDA approval.

E. Novel Approaches NA

F. Any Special Product Quality Labeling Recommendations

1) Within Section 11 we recommend that full names be used rather than the acronyms, FTC, RPV, and TAF.
2) We recommend this wording within Section 11, "*Rilpivirine*: The chemical name of rilpivirine hydrochloride drug substance is…"
3) We note that the list of active ingredients in the Patient Information section includes the counterions (rilpivirine hydrochloride and tenofovir alafenamide fumarate), which was not the case for the Genvoya tablet.
4) The inactive ingredient [redacted] (b) (4) is incorrectly included in Section 11 and should be deleted. The list of inactive ingredients in the Patient Information section is correct.
5) In the list of inactive ingredients in Section 11 polysorbate (b) (4) should come before povidone. The Patient Information section is correct.
6) At an appropriate time, please submit container/carton labels for (b) (4) the US (b) (4) products with "Tradename" replaced as appropriate.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

NDA 208351 is recommended for approval with one PMC from the Product Quality Perspective.

Stephen Miller -S

Digitally signed by Stephen Miller -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stephen Miller -S, 0.9.2342.19200300.100.1.1=1300087013
Date: 2016.02.03 20:26:32 -05'00'

Stephen Miller, Ph.D.; CMC-Lead; Branch 3; Division of New Drug Products I

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. The manufacturing facilities for NDA 208351 are found to be acceptable.

Rose Xu, facility reviewer, February 3, 2016

Secondary Review Comments and Concurrence:

I concur with this acceptable recommendation.

Christina Capacci-Daniel, Ph.D. – Feb. 3, 2016
Acting QAL/Consumer Safety Officer, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Review: The Biopharmaceutics review focuses on the evaluation and acceptability of the dissolution methods and acceptance criteria.

12. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes.

The in-vitro dissolution test methods are acceptable.

The revised dissolution acceptance criterion of Q= (b)(4)% at 20 minutes for emtricitabine (FTC) and tenofovir alafenamide (TAF) is acceptable and was agreed with the Applicant during a T-con between FDA and the Applicant on 12/3/15.

However, the dissolution acceptance criterion for rilpivirine (RPV) could not be agreed upon during the T-con on 12/3/15. For RPV, based on FDA's information request dated 12/8/16, the Applicant agreed (in a response dated 1/4/16) to an **interim rilpivirine dissolution acceptance criterion** of Q= (b)(4)% at 45 minutes and also agreed to a Post-Marketing Commitment [PMC] to compare dissolution results from all commercial batches at the 30-minute and 45-minute time points. In addition, the Applicant agreed to provide the requested information as a supplement 18 months post NDA approval.

12.1. What are the highlights of the chemistry and what are the physico-chemical properties of the drug substances (e.g. solubility) and formulation of the drug product?

Emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) fixed-dose combination (FDC) tablets are an immediate-release tablet dosage form containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV), and 25 mg of tenofovir alafenamide (TAF). The drug product is formulated as a

(b) (4)

(b) (4) F/R/TAF tablets are gray, h "GSI" on one side and "255" on the other.

(b) (4)

(b) (4)

[redacted]

12.2. Is there any information on the BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

The intrinsic solubility of FTC free base is (b) (4) [redacted] The Applicant states that FTC is considered to be a BCS Class 1 compound with high solubility across the physiologic pH range and high permeability observed in human clinical studies; however, an official designation is not requested in this NDA.

RPV HCl is practically (b) (4) [redacted] The Applicant states that RPV HCl is considered to be a BCS Class 2 compound with low solubility across the physiological pH range

and high permeability; however, an official designation is not requested in this NDA.

TAF exhibits (b) (4) The Applicant states that TAF fumarate is considered to be a BCS Class 3 compound with high solubility over the physiological pH range and low permeability; however, an official designation is not requested in this NDA.

12.3. Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant's claim?

N/A. Emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) fixed-dose combination (FDC) tablets are an immediate-release dosage form.

12.4. What are the proposed dissolution methods?

The Applicant proposed two different dissolution methods for release and stability testing of emtricitabine/rilpivirine/tenofovir alafenamide film-coated tablets (F/R/TAF tablets).
One method (b) (4) is to evaluate the dissolution of emtricitabine (FTC) and tenofovir alafenamide (TAF). The second method (b) (4) is to evaluate the dissolution of rilpivirine (RPV). The dissolution method parameters for both methods are provided below:

Table 12.1: Dissolutoin method, (b) (4), for emtricitabine (FTC) and tenofovir alafenamide (TAF)

USP apparatus	Apparatus 2 (paddle)
Medium	pH 5.5, 50 mM Sodium Citrate @37°C
Volume	500 mL
Rotation speed	75 rpm

Table 12.2: Dissolutoin method, (b) (4), for rilpivirine (RPV)

USP apparatus	Apparatus 2 (paddle)
Medium	0.5% Polysorbate 20 in 0.01 N HCl, pH 2.0 @37°C

Volume	(b) (4) mL
Rotation speed	75 rpm

12.5. What data are provided to support the adequacy of the proposed dissolution method?

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Recommendation and Signature:

Dissolution method: ACCEPTABLE

The following proposed dissolution methods are acceptable:

For emtricitabine (FTC) and tenofovir alafenamide (TAF):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	500 mL	pH 5.5, 50 mM Sodium Citrate @37.0± 0.5° C	UPLC/UV λ= (b) (4) nm

For Rilpivirine (RPV):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	1000 mL	0.5% Polysorbate 20 in 0.01 N HCl, pH 2 @37.0± 0.5° C	UPLC/UV λ= (b) (4) nm

Dissolution Acceptance Criterion: ACCEPTABLE WITH PMC

The dissolution acceptance criterion Q= (b) (4)% at 20 minutes for Emtricitabine (FTC) and Tenofovir Alafenamide (TAF) is acceptable.

For rilpivirine (RPV): the Applicant agreed to an **interim rilpivirine dissolution acceptance criterion** of Q= (b) (4)% at 45 minutes and also agreed to a Post-Marketing Commitment [PMC] to compare dissolution results from all commercial batches at the 30-minute and 45-minute time points. In addition, the Applicant agreed to provide the requested information as a supplement 18 months post NDA approval

Recommendation:

The recommendation for NDA 208351 for emtricitabine/ rilpivirine/tenofovir alafenamide tablets (200/25/25 mg) is **APPROVAL WITH PMC** from a Biopharmaceutics perspective.

1/28/16

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Concurrence and Signature:
I concur with Dr. Anand's assessment and recommendation.

1/28/16

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

14. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:
The emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) tablets are a solid oral dosage form and the container closure system includes silica gel desiccant [redacted] (b) (4) [redacted] (b) (4) (Section 3.2.P.7). F/R/TAF tablets are therefore not expected to promote microbial growth during the product shelf-life. During development, microbiological examination tests were performed at drug product release and stability to provide assurance of the absence of microbial contamination. Batch release data summarized in Section 3.2.P.5.4 show the microbial burden to be below the specification limits. Additionally, stability data show that F/R/TAF tablets met the microbial burden acceptance criteria following 6 months storage at the accelerated storage condition of 40 °C/75% RH as discussed in Section 3.2.P.8.1.

Reviewer's Assessment: Acceptable

To assure drug product safety and confirm no microbial contamination during drug product manufacturing process, microbial examination will be tested [redacted] (b) (4) [redacted] (b) (4) to the acceptance criteria established per harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 for the [redacted] (b) (4) commercial and [redacted] (b) (4) commitment lots of drug product (Section 3.2.P.8.2).

2.3.P.7 Container/Closure System

15. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

16. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Lactose monohydrate used in the manufacture of F/R/TAF tablets (b) (4) (b) (4) (b) (4) Lactose monohydrate (b) (4) are not covered by the requirements of guidelines on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. A letter of confirmation from the current supplier of lactose monohydrate is provided. Equivalent documentation will be obtained if alternate supplies are selected and used.

Reviewer's Assessment: Acceptable

The supplied information from vendor of Lactose Monohydrate USP was reviewed and deemed acceptable.

17. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:
Lactose monohydrate USP is used in the manufacture of F/R/TAF tablets and is tested to USP standards.

Reviewer's Assessment: Acceptable

Lactose monohydrate is the only material in the drug product derived from biological sources. The USP testing performed on the material includes Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommend Approval for Microbiology

Steven Frisbee 11/24/2015

The drug product is a solid oral dosage form that uses standard pharmaceutical excipients and manufacturing processes, including (b) (4) processes (b) (4) and tablet film coating). There is adequate data and justification for not performing routine microbial testing for the drug product. To assure drug product safety and confirm no microbial contamination during drug product manufacturing process, microbial

examination will be tested (b) (4) to the acceptance criteria established per harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 for the (b) (4) commercial and (b) (4) commitment lots of drug product.

Secondary Review Comments and Concurrence:

I concur.

Akm Khairuzzaman, Ph.D. 11/25/2015
Branch Chief (Acting)
Branch I, Div I,
Office of Process & Facility (OPF)

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant requests a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the concentration of emtricitabine, rilpivirine, and tenofovir alafenamide in the aquatic environment is expected to be less than 1 part per billion. No special circumstances are known to exist.

Reviewer's Assessment: Adequate. James Laurenson (OPQ/ONDP) states that the claim is reasonable and should be accepted (e-mail of 9/1/15).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
From the product quality perspective this application is recommended for approval.

George Lunn, Ph.D. Nov 30, 2015
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Nov 30, 2015
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

[TRADENAME]™ (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: YYYY

-----DOSAGE FORMS AND STRENGTHS-----
Tablets: 200 mg of FTC, 25 mg of RPV and 25 mg of TAF. (3)

"Highlights" Section (21CFR 201.57(a

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	[TRADENAME]™ (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use	Adequate
Dosage form, route of administration	Oral	Adequate
Controlled drug substance symbol (if applicable)	NA	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 200 mg of FTC, 25 mg of RPV and 25 mg of TAF	Adequate The acronym, TAF, is used throughout the PI for the recently approved Genvoya tablet.

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

Each [TRADENAME] tablet contains 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV) (equivalent to 27.5 mg of rilpivirine hydrochloride), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).

The tablets are gray, capsule-shaped, film-coated and debossed with "GSI" on one side and "255" on the other side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV) (equivalent to 27.5 mg of rilpivirine hydrochloride), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The tablets are gray, capsule-shaped, film-coated and debossed with "GSI" on one side and "255" on the other side.	Adequate

Conclusion:Adequate

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

[TRADENAME] is a fixed-dose combination tablet containing FTC, RPV, and TAF for oral administration.

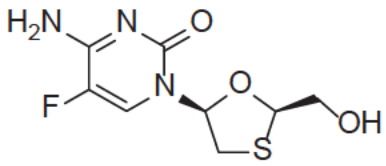
- FTC is a synthetic nucleoside analog of cytidine.

- RPV is a non-nucleoside reverse transcriptase inhibitor. [redacted]
- TAF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each [redacted] tablet contains 200 mg of FTC, 25 mg of RPV (equivalent to 27.5 of rilpivirine hydrochloride) and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate). [redacted] the following inactive ingredients: croscarmellose sodium, [redacted], lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and polysorbate 20. The tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

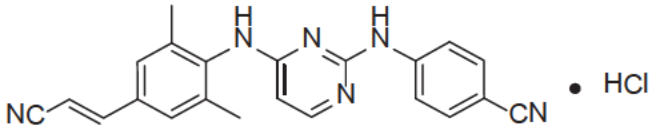
Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1*H*)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

[redacted] has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 [redacted] has the following structural formula:



FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

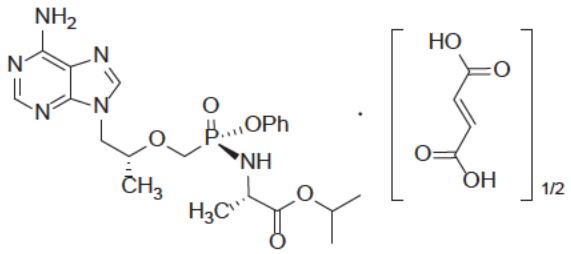
Rilpivirine: [redacted] The chemical name for [redacted] hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \bullet HCl$ and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

(b) (4) has a molecular formula of $C_{23}H_{31}O_7N_6P$ and a molecular weight of 534.5. (b) (4) has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	[TRADENAME] is a fixed-dose combination tablet containing FTC, RPV, and TAF for oral administration	Adequate
Dosage form and route of administration	Tablet, oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each (b) (4) tablet contains 200 mg of FTC, 25 mg of RPV (equivalent to 27.5 of rilpivirine hydrochloride) and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	(b) (4) the following inactive ingredients: croscarmellose sodium, (b) (4), lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and polysorbate 20. The tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.	(b) (4) Polysorbate (b) (4) should come before povidone in the list.
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor, and is indicated for use as a complete regimen for the treatment of HIV-1 infection in (b) (4) patients 12 years of age and older with no antiretroviral treatment history or who are virologically suppressed to replace (b) (4) antiretroviral (b) (4) regimen	Adequate
Chemical name, structural formula, molecular weight	Present, see above	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Present, see above	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

[TRADENAME] (b) (4) tablets are gray, capsule-shaped, and film coated with "GSI" debossed on one side and "255" on the other side. Each bottle contains 30 tablets (NDC 61958-xxxx-x), a silica gel desiccant, and a polyester coil, and is closed with a child-resistant closure.

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

(b) (4)

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(b) (4)	Adequate
Available units (e.g., bottles of 100 tablets)	Each bottle contains 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Gray, capsule-shaped, and film coated tablets with "GSI" debossed on one side and "255" on the other side	Adequate
Special handling (e.g., protect from light, do not freeze)	Keep container tightly closed. Dispense only in original container	Adequate
Storage conditions	Store below 30 °C (86 °F)	Adequate

#17: Patient Counseling Information and Patient Information Sections

Item	Information Provided in NDA	Reviewer's Assessment
How should I store [TRADENAME]?	• Store [TRADENAME] below 86 °F (30 °C). • Keep [TRADENAME] in its original container. • Keep the container tightly closed. (b) (4)	Adequate

	Keep [TRADENAME] and all medicines out of reach of children.	
What are the ingredients in [TRADNAME]?	**Active ingredients:** emtricitabine, rilpivirine hydrochloride, and tenofovir alafenamide fumarate. **Inactive ingredients:** croscarmellose sodium, lactose monohydrate, and magnesium stearate, microcrystalline cellulose, polysorbate 20,povidone. The tablet film coating contains iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.	Listing counterions could be confusing to patients.
Manufacturer/distributor name (21 CFR 201.1)	Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404.	Adequate, at end of Patient Information (PPI) only

Conclusion: Adequate. Tenofovir alafenamide fumarate is only used in the context of the physical drug substance or the equivalency statement. Otherwise the name tenofovir alafenamide is used in line with current thinking. Similary approaches are taken for rilpivirine hydrochloride and rilpivirine throughout the Prescribing Information.

Comments for consideration during labeling:

- Within Section 11 we recommend that full names be used rather than the acronyms, FTC, RPV, and TAF.
- We recommend this wording within Section 11, "*Rilpivirine*: The chemical name of rilpivirine hydrochloride drug substance is…"
- We note that the list of active ingredients in the Patient Information section includes the counterions (rilpivirine hydrochloride and tenofovir alafenamide fumarate), which was not the case for the Genvoya tablet.
- The inactive ingredient [redacted] (b) (4) is incorrectly included in Section 11 and should be deleted. However, the list of inactive ingredients in the Patient Information section is correct.
- In section 11 polysorbate (b) (4) should come before povidone. The Patient Information section is correct.

2. Container and Carton Labeling

1) Immediate Container Label

The US container label is as follows.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Assessment:

Immediate Container Label

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tradename (emtricitabine, rilpivirine tenofovir alafenamide) Tablets 200 mg/25 mg/25 mg	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	200 mg/25 mg/25 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	NA	
Net contents* (21 CFR 201.51(a))	30 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Store below 30 °C (86 °F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404. Made in Canada	Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Carton Labeling

(b) (4)

(b) (4)

[redacted]

Conclusion: Adequate . Comments for consideration during labeling:

At an appropriate time, please submit container/carton labels for (b) (4) the US (b) (4) products with "Tradename" replaced as appropriate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
The current labeling is adequate for approval, and recommendations for consideration as labeling is finalized have been included in the executive summary section.

George Lunn, Ph.D. Nov 30, 2015
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Nov 30, 2015
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ

II. List of Deficiencies To Be Communicated

Drug Substance
Drug Product
Process
Facility
Biopharmaceutics
Microbiology
Environmental
Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability	(b) (4)	L	Expiration dating period (b) (4)	L	The studies on tablets made from (b) (4)
Physical stability (solid state)	Initial risk due to multiple solid-state forms for all actives Severity set by low solubility rilpivirine	M	(b) (4)	L	
Content uniformity	(b) (4)	L	(b) (4)	L	(b) (4)
Microbial limits	Microbial Limits testing in DP spec	L		L	
Dissolution – BCS Class I & III	Both Emtricitabine and TAF are high soluble compounds.	L	(b) (4)	L	(b) (4)
Dissolution – BCS Class II & IV	Rilpivirine has low solubility	M	(b) (4) Dissolution testing method (b) (4) is well justified.	M	RPV is a BCS II compound with poor solubility and the effect of (b) (4) is critical.
Tablet (b) (4) **content**	(b) (4)	M	(b) (4)	L	(b) (4)
	(b) (4)	L	(b) (4)	L	

(b) (4)			(b) (4)		
Drug Product Impurity Control		L	No evidence of theoretical effect of TAF fumarate on stability of Emtricitabine	L	
Patient Use Issues	Tablets are medium size (15 mm long x 7 mm wide); no (b) (4) or dispersing instructions	L		L	

Recommendation:
NDA: Recommendation pending at this time

NDA 208351
Review 1
Review Date: December 4, 2015

Drug Name/Dosage Form	emtricitabine/rilpivirine/tenofovir alafenamide
Strength	200mgFCT/25mgRPV/25mgTAF
Route of Administration	PO
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	01-Jul-2015
Amendment	06-Aug-2015
Amendment	24-Sep-2015
Amendment	16-Oct-2015
Amendment	13-Oct-2015
Amendment	13-Nov-2015
Amendment	30-Nov-2015

Quality Review Team

Responsibility	Primary Reviewer
RBPM	Florence Aisida
Drug Substance	Haripada Sarker
Drug Product	George Lunn
Drug Process	Steven Frisbee
Biopharmaceutics	Om Anand
Facility	Rose Xu
EA	James Laurenson
ORA Contact	Paul Perdue, Jr.
ATL	Stephen Miller

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS
(b) (4) [redacted]	II	[redacted]	[redacted] (b) (4)	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	IV	[redacted]	[redacted]	Adequate
[redacted]	IV	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]	III	[redacted]	[redacted]	Adequate
[redacted]		[redacted]	[redacted]	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	123098	IND for this combination during development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical		See separate review		
Environmental Assessment	AC	J.Laurenson provided input to G.Lunn's review	Sept 1, 2015	G.Lunn
Other	NA			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the quality of the drug substances and this drug product, with the following exceptions. At this time the assessment of the manufacturing facilities is not yet complete. The dissolution methods are acceptable; however the acceptance criterion for rilpivirine has not yet been finalized.

NDA 208351 cannot be recommended for approval until the assessment of the (b) (4) (b) (4) facilities are completed, and the dissolution acceptance criterion for rilpivirine is finalized.

Labeling recommendations from the Product Quality perspective have been provided to the OND PM, for consideration during final labeling.

1. Summary of Complete Response issues NA
2. Action letter language, related to critical issues such as expiration date

We also acknowledge receipt of information related to ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide), 200/25/25 mg fixed-dose combination tablet for your Gilead Access Program that was reviewed as part of this application.

3. Benefit/Risk Considerations

Evaluation of the quality aspects of Odefsey tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [Tenofovir Alafenamide Fumarate] Quality Summary

Information Relevant to Impurity Control: Maximum Daily Dose of TAF fumarate is 25 mg/day for patients using this product. Acceptable Intake of Mutagenic Impurities: (b) (4) (b) (4) at 25 mg/day maximum dose = (b) (4) % for TAF fumarate. (b) (4) (b) (4) (b) (4)

For additional drug substance information, see NDA 207561 and detailed review notes, below.

A. Drug Substance [Emtricitabine] Quality Summary

See NDA 21752 and detailed review notes, below.

A. Drug Substance [Rilpivirine Hydrochloride] Quality Summary

See NDA 202022, DMF (b) (4), and detailed review notes, below.

B. Drug Product [Emtricitabine, Rilpivirine and Tenofovir Alafenamide Tablets] Quality Summary

1) Strength: 200mg / 25mg / 25mg
2) Description/Commercial Image of US Product: gray capsule-shaped film-coated (b) (4) tablets debossed with "GSI" on one side and "255" on the other. Description/Commercial Image of Access Product: (b) (4) - (b) (4).
3) Summary of Product Design: The product is a (b) (4) tablet with three drug substances, and is produced using (b) (4) processes. The specification includes tests for appearance, identity, (b) (4) assay, degradants, uniformity, dissolution, and microbial limits. The specification is largely (b) (4) for an immediate release solid oral dosage form and a satisfactory justification is provided. After extensive discussion the (b) (4) (b) (4) NMT (b) (4) %. The degradants are toxicologically qualified at the proposed limits. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust. Satisfactory batch analyses are provided for 12 batches of (b) (4).
4) List of Excipients: lactose monohydrate, microcrystalline cellulose, povidone, polysorbate 20, croscarmellose sodium, magnesium stearate, and (b) (4) (b) (4) The magnesium stearate is from (b) (4) sources and the lactose (b) (4) ray (b) (4) (b) (4) film coats are used. All excipients and the components of the film coat are compendial.
5) Process Selection (Unit Operations Summary):
   i. (b) (4)
   ii.
   iii.
   iv. Critical equipment: None.
6) Container Closure: The tablets are packaged 30 count in 75 mL white HDPE bottles containing (b) (4) of silica gel desiccant and a polyester coil. The bottles are capped with (b) (4) screw caps and an induction seal.

7) Expiration Date & Storage Condition: The applicant claims a 24 month expiration dating period with the storage statement: "Store below 30°C". This is supported with a statistical analysis of the available stability data, including the 30°C/75% RH long-term data, and is reasonable. The expiration dating period (b) (4) (b) (4).

Twelve months of satisfactory stability data are provided for one batch and 9 months for 2 batches stored at 25°C/60% RH and 30°C/75% RH as well as 6 months for 3 batches stored at 40°C/75% RH. Lesser amounts of stability data are provided for other batches. There are no out of specification results. The only obvious trends are an increase in TAF impurities (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) There is an (b) (4) (b) (4) Data (b) (4) (b) (4). This is why it is important to (b) (4) NMT (b) (4)%. There is no obvious trend in dissolution. The stability behavior of the gray (b) (4) tablets appears to be equivalent. The applicant reports a (b) (4) in TAF assay.

8) List of Co-Packaged Components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Odefsey Tablets
Non Proprietary Name of the Drug Product	Emtricitabine, Rilpivirine and Tenofovir Alafenamide Tablets
Non Proprietary Name of the Drug Substance	Emtricitabine; Rilpivirine Hydrochloride; Tenofovir Alafenamide Fumarate
Proposed Indication(s) including Intended Patient Population	Complete regimen for the treatment of HIV-1 infection in (b) (4) patients 12 years of age and older
Duration of Treatment	Chronic (classified as 1-10 years of use for purposes of setting limits on mutagenic impurities per ICH M7)
Maximum Daily Dose	1 tablet per day
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance: An official designation has not been requested, however, the Applicant considers emtricitabine (FTC) to be a BCS Class 1 compound, rilpivirine hydrochloride (RPV) to be a BCS Class 2 compound and tenofovir alafenamide (TAF) to be a BCS Class 3 compound.
   - Drug Product: An official designation has not been requested for this combination drug product containing BCS Class 1, 2 and 3 drug substances.

2. Biowaivers/Biostudies:
   - PK studies: **Study GS-US-366-1159** (OCP is reviewing this study)
   - Biowaiver Requests: Not Applicable
   - IVIVC: Not Applicable

3. Dissolution method: **ACCEPTABLE**
   - The following proposed dissolution methods are acceptable:

   For emtricitabine (FTC) and tenofovir alafenamide (TAF):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	500 mL	pH 5.5, 50 mM Sodium Citrate @37.0± 0.5° C	UPLC/UV λ=(b) (4) nm

   For rilpivirine (RPV):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	1000 mL	0.5% Polysorbate 20 in 0.01 N HCl, pH 2 @37.0± 0.5° C	UPLC/UV λ=(b) (4) nm

4. **Dissolution Acceptance Criterion: Pending**
   The revised dissolution acceptance criterion of Q=(b) (4)% at 20 minutes for emtricitabine (FTC) and tenofovir alafenamide (TAF) is acceptable and was agreed with the Applicant during a T-con between FDA and the Applicant on 12/3/15.

   However, the dissolution acceptance criterion for rilpivirine (RPV) could not be agreed upon during the T-con on 12/3/15, therefore a final decision regarding the acceptance criterion for RPV is PENDING further review, based on the discussion with the Applicant.

E. Novel Approaches NA

F. Any Special Product Quality Labeling Recommendations

1) Within Section 11 we recommend that full names be used rather than the acronyms, FTC, RPV, and TAF.
2) We recommend this wording within Section 11, "*Rilpivirine*: The chemical name of rilpivirine hydrochloride drug substance is…"

3) We note that the list of active ingredients in the Patient Information section includes the counterions (rilpivirine hydrochloride and tenofovir alafenamide fumarate), which was not the case for the Genvoya tablet.
4) The inactive ingredient (b) (4) is incorrectly included in Section 11 and should be deleted. The list of inactive ingredients in the Patient Information section is correct.
5) In the list of inactive ingredients in Section 11 polysorbate (b) (4) should come before povidone. The Patient Information section is correct.
6) At an appropriate time, please submit container/carton labels for (b) (4) the US (b) (4) (b) (4) products with "Tradename" replaced as appropriate.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

NDA 208351 cannot be recommended for approval until the assessment of the (b) (4) facilities are completed, and the dissolution acceptance criterion for rilpivirine is finalized.

Stephen Miller -S

Digitally signed by Stephen Miller -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stephen Miller -S, 0.9.2342.19200300.100.1.1=1300087013
Date: 2015.12.04 15:14:20 -05'00'

Stephen Miller, Ph.D.; CMC-Lead; Branch 3; Division of New Drug Products I

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(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

All facility evaluations are complete and acceptable, except the two drug product manufacturers: (b) (4) (b) (4)

The inspection report for (b) (4) **was just sent to OPF/DIA for review on** (b) (4)**, but the inspection report for** (b) (4) **has not yet been completed. The facility recommendation for each of these drug product manufacturing sites cannot be entered until the review of each inspection reports has been completed and the cases in CMS are closed.**

In addition, an Advice letter to the Applicant will be sent shortly. This letter (b) (4)

The completed Overall Facility Assessment will be provided as an addendum to this review at a later date.

Rose Xu 12/1/2015

Secondary Review Comments and Concurrence:

I concur with this interim Facility Assessment. An addendum review is required.

Christina Capacci-Daniel, Ph.D. – Dec. 1, 2015
Acting QAL/Consumer Safety Officer, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Review: The Biopharmaceutics review focuses on the evaluation and acceptability of the dissolution methods and acceptance criteria.

12. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

NO.
The in-vitro dissolution test methods are acceptable.

The revised dissolution acceptance criterion of Q= (b) (4)% at 20 minutes for emtricitabine (FTC) and tenofovir alafenamide (TAF) is acceptable and was agreed with the Applicant during a T-con between FDA and the Applicant on 12/3/15.

However, the dissolution acceptance criterion for rilpivirine (RPV) could not be agreed upon during the T-con on 12/3/15, therefore a final decision regarding the acceptance criterion for RPV is PENDING further review, based on the discussion with the Applicant.

12.1. What are the highlights of the chemistry and what are the physico-chemical properties of the drug substances (e.g. solubility) and formulation of the drug product?

Emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) fixed-dose combination (FDC) tablets are an immediate-release tablet dosage form containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV), and 25 mg of tenofovir alafenamide (TAF) (b) (4)

(b) (4)

(b) (4) F/R/TAF tablets are gray, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "255" on the other.

(b) (4)

(b) (4)

12.2. Is there any information on the BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

The intrinsic solubility of FTC free base is (b) (4) The Applicant states that FTC is considered to be a BCS Class 1 compound with high solubility across the physiologic pH range and high permeability observed in human clinical studies; however, an official designation is not requested in this NDA.

RPV HCl is practically (b) (4) (b) (4) (b) (4) The Applicant states that RPV HCl is considered to be a BCS Class 2 compound with low solubility across the physiological pH range and high permeability; however, an official designation is not requested in this NDA.

TAF exhibits [redacted] The Applicant states that TAF fumarate is considered to be a BCS Class 3 compound with high solubility over the physiological pH range and low permeability; however, an official designation is not requested in this NDA.

12.3. Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant's claim?

N/A. Emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) fixed-dose combination (FDC) tablets are an immediate-release dosage form.

12.4. What are the proposed dissolution methods?

The Applicant proposed two different dissolution methods for release and stability testing of emtricitabine/rilpivirine/tenofovir alafenamide film-coated tablets (F/R/TAF tablets).
One method [redacted] is to evaluate the dissolution of emtricitabine (FTC) and tenofovir alafenamide (TAF). The second method [redacted] is to evaluate the dissolution of rilpivirine (RPV). The dissolution method parameters for both methods are provided below:

Table 12.1: Dissolutoin method, [redacted], for emtricitabine (FTC) and tenofovir alafenamide (TAF)

USP apparatus	Apparatus 2 (paddle)
Medium	pH 5.5, 50 mM Sodium Citrate @37°C
Volume	500 mL
Rotation speed	75 rpm

Table 12.2: Dissolutoin method, [redacted], for rilpivirine (RPV)

USP apparatus	Apparatus 2 (paddle)
Medium	0.5% Polysorbate 20 in 0.01 N HCl, pH 2.0 @37°C
Volume	[redacted] mL
Rotation speed	75 rpm

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Recommendation and Signature:

Dissolution method: ACCEPTABLE

The following proposed dissolution methods are acceptable:

For emtricitabine (FTC) and tenofovir alafenamide (TAF):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	500 mL	pH 5.5, 50 mM Sodium Citrate @37.0± 0.5° C	UPLC/UV λ=(b) (4) nm

For Rilpivirine (RPV):

Apparatus	Speed	Volume	Medium	Detection
USP 2 (paddle)	75 rpm	1000 mL	0.5% Polysorbate 20 in 0.01 N HCl, pH 2 @37.0± 0.5° C	UPLC/UV λ= (b) (4) nm

Dissolution Acceptance Criterion: PENDING

The dissolution acceptance criterion Q= (b) (4)% at 20 minutes for Emtricitabine (FTC) and Tenofovir Alafenamide (TAF) is acceptable. However, The FDA and the Applicant could not agree on the acceptance criterion for rilpivirine (RPV). Therefore, the dissolution acceptance criterion for RPV is still under review, based on the discussion with the Applicant during the T-con on 12/3/15.

Recommendation:

At this time (GRMP date) the recommendation for NDA 208351 for emtricitabine/ rilpivirine/tenofovir alafenamide tablets (200/25/25 mg) is **PENDING** from a Biopharmaceutics perspective.

12/3/15

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Concurrence and Signature:
I concur with Dr. Anand's assessment and recommendation.

12/3/15

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

14. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:
The emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) tablets are a solid oral dosage form and the container closure system includes silica gel desiccant [redacted] (b) (4) [redacted] (b) (4) (Section 3.2.P.7). F/R/TAF tablets are therefore not expected to promote microbial growth during the product shelf-life. During development, microbiological examination tests were performed at drug product release and stability to provide assurance of the absence of microbial contamination. Batch release data summarized in Section 3.2.P.5.4 show the microbial burden to be below the specification limits. Additionally, stability data show that F/R/TAF tablets met the microbial burden acceptance criteria following 6 months storage at the accelerated storage condition of 40 °C/75% RH as discussed in Section 3.2.P.8.1.

Reviewer's Assessment: Acceptable

To assure drug product safety and confirm no microbial contamination during drug product manufacturing process, microbial examination will be tested [redacted] (b) (4) [redacted] (b) (4) to the acceptance criteria established per harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 for the [redacted] (b) (4) commercial and [redacted] (b) (4) commitment lots of drug product (Section 3.2.P.8.2).

2.3.P.7 Container/Closure System

15. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

16. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Lactose monohydrate used in the manufacture of F/R/TAF tablets (b) (4) (b) (4) (b) (4) Lactose monohydrate (b) (4) are not covered by the requirements of guidelines on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. A letter of confirmation from the current supplier of lactose monohydrate is provided. Equivalent documentation will be obtained if alternate supplies are selected and used.

Reviewer's Assessment: Acceptable

The supplied information from vendor of Lactose Monohydrate USP was reviewed and deemed acceptable.

17. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:
Lactose monohydrate USP is used in the manufacture of F/R/TAF tablets and is tested to USP standards.

Reviewer's Assessment: Acceptable

Lactose monohydrate is the only material in the drug product derived from biological sources. The USP testing performed on the material includes Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommend Approval for Microbiology

Steven Frisbee 11/24/2015

The drug product is a solid oral dosage form that uses standard pharmaceutical excipients and manufacturing processes, including (b) (4) processes (b) (4) and tablet film coating). There is adequate data and justification for not performing routine microbial testing for the drug product. To assure drug product safety and confirm no microbial contamination during drug product manufacturing process, microbial

examination will be tested (b) (4) to the acceptance criteria established per harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 for the (b) (4) commercial and (b) (4) commitment lots of drug product.

Secondary Review Comments and Concurrence:

I concur.

Akm Khairuzzaman, Ph.D. 11/25/2015
Branch Chief (Acting)
Branch I, Div I,
Office of Process & Facility (OPF)

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant requests a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the concentration of emtricitabine, rilpivirine, and tenofovir alafenamide in the aquatic environment is expected to be less than 1 part per billion. No special circumstances are known to exist.

Reviewer's Assessment: Adequate. James Laurenson (OPQ/ONDP) states that the claim is reasonable and should be accepted (e-mail of 9/1/15).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
From the product quality perspective this application is recommended for approval.

George Lunn, Ph.D. Nov 30, 2015
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Nov 30, 2015
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

[TRADENAME]™ (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: YYYY

-----DOSAGE FORMS AND STRENGTHS-----
Tablets: 200 mg of FTC, 25 mg of RPV and 25 mg of TAF. (3)

"Highlights" Section (21CFR 201.57(a

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	[TRADENAME]™ (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use	Adequate
Dosage form, route of administration	Oral	Adequate
Controlled drug substance symbol (if applicable)	NA	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 200 mg of FTC, 25 mg of RPV and 25 mg of TAF	Adequate The acronym, TAF, is used throughout the PI for the recently approved Genvoya tablet.

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

Each [TRADENAME] tablet contains 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV) (equivalent to 27.5 mg of rilpivirine hydrochloride), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).

The tablets are gray, capsule-shaped, film-coated and debossed with "GSI" on one side and "255" on the other side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV) (equivalent to 27.5 mg of rilpivirine hydrochloride), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The tablets are gray, capsule-shaped, film-coated and debossed with "GSI" on one side and "255" on the other side.	Adequate

Conclusion:Adequate

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

[TRADENAME] is a fixed-dose combination tablet containing FTC, RPV, and TAF for oral administration.

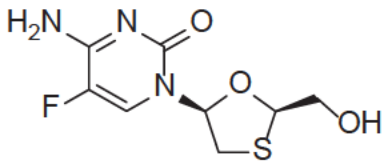
- FTC is a synthetic nucleoside analog of cytidine.

- RPV is a non-nucleoside reverse transcriptase inhibitor. [redacted]
- TAF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each [redacted] mg tablet contains 200 mg of FTC, 25 mg of RPV (equivalent to 27.5 of rilpivirine hydrochloride) and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate). [redacted] the following inactive ingredients: croscarmellose sodium, [redacted], lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and polysorbate 20. The tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

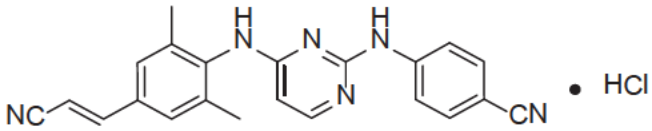
Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1*H*)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

[redacted] has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. [redacted] has the following structural formula:



FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

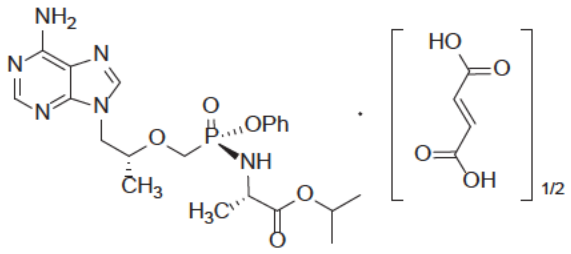
Rilpivirine: [redacted]. The chemical name for [redacted] hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \bullet HCl$ and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

Tenofovir Alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

(b) (4) has a molecular formula of $C_{23}H_{31}O_7N_6P$ and a molecular weight of 534.5 (b) (4) has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	[TRADENAME] is a fixed-dose combination tablet containing FTC, RPV, and TAF for oral administration	Adequate
Dosage form and route of administration	Tablet, oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each (b) (4) tablet contains 200 mg of FTC, 25 mg of RPV (equivalent to 27.5 of rilpivirine hydrochloride) and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	(b) (4) the following inactive ingredients: croscarmellose sodium, (b) (4), lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and polysorbate 20. The tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.	(b) (4) Polysorbate (b) (4) should come before povidone in the list.
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor, and is indicated for use as a complete regimen for the treatment of HIV-1 infection in (b) (4) patients 12 years of age and older with no antiretroviral treatment history or who are virologically suppressed to replace (b) (4) antiretroviral (b) (4) regimen	Adequate
Chemical name, structural formula, molecular weight	Present, see above	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Present, see above	Adequate

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

[TRADENAME] (b) (4) mg tablets are gray, capsule-shaped, and film coated with "GSI" debossed on one side and "255" on the other side. Each bottle contains 30 tablets (NDC 61958-xxxx-x), a silica gel desiccant, and a polyester coil, and is closed with a child-resistant closure.

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

(b) (4)

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(b) (4)	Adequate
Available units (e.g., bottles of 100 tablets)	Each bottle contains 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Gray, capsule-shaped, and film coated tablets with "GSI" debossed on one side and "255" on the other side	Adequate
Special handling (e.g., protect from light, do not freeze)	Keep container tightly closed. Dispense only in original container	Adequate
Storage conditions	Store below 30 °C (86 °F)	Adequate

#17: Patient Counseling Information and Patient Information Sections

Item	Information Provided in NDA	Reviewer's Assessment
How should I store [TRADENAME]?	• Store [TRADENAME] below 86 °F (30 °C). • Keep [TRADENAME] in its original container. • Keep the container tightly closed. (b) (4)	Adequate

	Keep [TRADENAME] and all medicines out of reach of children.	
What are the ingredients in [TRADNAME]?	**Active ingredients:** emtricitabine, rilpivirine hydrochloride, and tenofovir alafenamide fumarate. **Inactive ingredients:** croscarmellose sodium, lactose monohydrate, and magnesium stearate, microcrystalline cellulose, polysorbate 20,povidone. The tablet film coating contains iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.	Listing counterions could be confusing to patients.
Manufacturer/distributor name (21 CFR 201.1)	Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404.	Adequate, at end of Patient Information (PPI) only

Conclusion: Adequate. Tenofovir alafenamide fumarate is only used in the context of the physical drug substance or the equivalency statement. Otherwise the name tenofovir alafenamide is used in line with current thinking. Similary approaches are taken for rilpivirine hydrochloride and rilpivirine throughout the Prescribing Information.

Comments for consideration during labeling:

- Within Section 11 we recommend that full names be used rather than the acronyms, FTC, RPV, and TAF.
- We recommend this wording within Section 11, "*Rilpivirine*: The chemical name of rilpivirine hydrochloride drug substance is…"
- We note that the list of active ingredients in the Patient Information section includes the counterions (rilpivirine hydrochloride and tenofovir alafenamide fumarate), which was not the case for the Genvoya tablet.
- The inactive ingredient [redacted] (b) (4) is incorrectly included in Section 11 and should be deleted. However, the list of inactive ingredients in the Patient Information section is correct.
- In section 11 polysorbate (b) (4) should come before povidone. The Patient Information section is correct.

2. Container and Carton Labeling

1) Immediate Container Label

The US container label is as follows.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Assessment:

Immediate Container Label

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tradename (emtricitabine, rilpivirine tenofovir alafenamide) Tablets 200 mg/25 mg/25 mg	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	200 mg/25 mg/25 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	NA	
Net contents* (21 CFR 201.51(a))	30 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Store below 30 °C (86 °F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404. Made in Canada	Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Carton Labeling

(b) (4)

(b) (4)

[redacted]

Conclusion: Adequate . Comments for consideration during labeling:

At an appropriate time, please submit container/carton labels for (b) (4) the US (b) (4) products with "Tradename" replaced as appropriate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
The current labeling is adequate for approval, and recommendations for consideration as labeling is finalized have been included in the executive summary section.

George Lunn, Ph.D. Nov 30, 2015
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Nov 30, 2015
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ

II. List of Deficiencies To Be Communicated

Drug Substance
Drug Product
Process
Facility
Biopharmaceutics
Microbiology
Environmental
Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability	(b) (4)	**L**	Expiration dating period (b) (4)	**L**	The studies on tablets made from (b) (4)
Physical stability (solid state)	Initial risk due to multiple solid-state forms for all actives Severity set by low solubility rilpivirine	**M**	(b) (4)	**L**	
Content uniformity	(b) (4)	**L**	(b) (4)	**L**	(b) (4)
Microbial limits	Microbial Limits testing in DP spec	**L**		**L**	
Dissolution – BCS Class I & III	Both Emtricitabine and TAF are high soluble compounds.	**L**		**L**	
Dissolution – BCS Class II & IV	Rilpivirine has low solubility	**M**		**L**	
Tablet (b) (4) (b) (4)	(b) (4)	**M**	(b) (4)	**L**	(b) (4)
	(b) (4)	**L**	(b) (4)	**L**	
Drug Product Impurity Control		**L**	No evidence of theoretical effect of TAF fumarate on stability of Emtricitabine	**L**	
Patient Use Issues	Tablets are medium size (15 mm long x 7 mm wide); no (b) (4) or dispersing instructions	**L**		**L**	

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

/s/

ROBYN S JORDON
03/09/2016