

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208464Orig1s000**

**CHEMISTRY REVIEW(S)**

Recommendation: **Approval**

**NDA 208464  
Review 1**

Drug Name/Dosage Form	TAF (tenofovir alafenamide)
Strength	25 mg tablet
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	11-Jan-2016	Prod Quality
Quality/Response to IR	27-Jan-2016	Prod Quality
Quality/Response to IR	25-Mar-2016	Prod Quality
Quality/Response to IR	03-May-2016	Prod Quality
Quality/Response to IR	08-Jun-2016	Prod Quality
Labeling Amendment	07-July-2016	All
Quality/Response to IR	05-Aug-2016	Prod Quality
Quality/Response to IR	09-Aug-2016	Prod Quality

**Quality Review Team**

Discipline	Reviewer	Secondary Reviewer
ATL	Stephen Miller	NA
Drug product	Yong Wang	Balajee Shanmugam
Biopharmaceutics	Jing Li	Elsbeth Chikhale
Process	Ying Wang	Upinder Atwal
Facilities	Frank Wackes	Christina Capacci-Daniel
RBPM	Florence (Bimidele) Aisida	NA

## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)	(b) (4)	AC		Sufficient information is provided in the NDA
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	
	Type III		AC		“	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND for this product	IND 115561	TAF for HBV
NDA for related product	NDA 207561	Approved TAF-Combination for HIV
NDA for related product	NDA 208215	Approved TAF-Combination for HIV
NDA for related product	NDA 208351	Approved TAF-Combination for HIV

## 2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

## Executive Summary

### I. Recommendations and Conclusion on Approvability

This NDA is recommended for Approval from the Product Quality perspective.

### II. Summary of Quality Assessments

#### A. Product Overview

Tenofovir Alafenamide Fumarate (TAF) has been developed as second prodrug of tenofovir. A notable advantage is the reduced dose of TAF (10-25 mg/day) compared to the original prodrug, tenofovir disoproxil fumarate (245 mg/day). Prodrugs of tenofovir have activity against both HIV and Hepatitis B viruses. Under this NDA the TAF 25mg tablet is proposed for treatment of chronic infection with the Hepatitis B Virus (HBV). An indication for HIV treatment is not proposed for this TAF-alone product, although there have been three previously-approved NDAs for tablets containing combinations of TAF and other anti-HIV drugs (Genvoya, Odefsey, and Descovy).

<b>Proposed Indication(s) including Intended Patient Population</b>	<i>Treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease.</i>
<b>Duration of Treatment</b>	<i>Chronic treatment</i>
<b>Maximum Daily Dose</b>	<i>1 tablet once per day (25 mg/day)</i>
<b>Alternative Methods of Administration</b>	<i>None</i>

#### B. Quality Assessment Overview

Drug substance information for this NDA is cross-referenced the approved Genvoya application (NDA 207561). As agreed during PreNDA discussions, selected information is provided in this NDA by hyperlinks to the Genvoya NDA. TAF drug substance is highly soluble by BCS criteria. It is manufactured as the (b) (4) (b) (4). The only significant drug substance aspect which needed to be re-evaluated under this NDA was the control strategy for mutagenic impurities. This was necessary because the threshold of toxicological concern (TTC) for the chronic HBV indication (1.5 ug/day; (b) (4) ug/day for (b) (4)) is lower than the TTC for the HIV indication (10 ug/day; (b) (4) ug/day for (b) (4)), because the length of dosing for HIV is generally limited by resistance development. Upon request, the applicant provided an evaluation of the control strategy, which showed that the process and controls during

the (b) (4) (Option 3 and Option 4 controls per ICH M7) will limit mutagenic impurities appropriately for the HBV indication (see the Justification of Specification section of the Dr. Yong Wang's drug product review for further information).

The drug product is an immediate-release tablet: yellow, round, film-coated tablets debossed with "GSI" on one side and "25" on the other side. It is a relatively small tablet 7.9 mm in diameter and weighing approximately 210 mg. TAF tablets are packaged in 60 mL white, high-density polyethylene (HDPE) bottles containing one (1) gram of silica gel desiccant, (b) (4), and a polyester coil. Each bottle contains thirty (30) tablets and is capped using a white, (b) (4) child-resistant (b) (4) screw cap with an induction-sealed, aluminum-faced liner. The NDA contains information from 7 pilot scale batches (b) (4) kg scale) and 1 commercial batch ((b) (4) kg; (b) (4) tablets). All batches were manufactured at the intended commercial facility (b) (4). The controls on the drug product quality are comparable to those of the earlier TAF tablets, and are appropriate for this product. The 24-month expiration dating period with labeling of "Store below 30 °C (86 °F)" is adequately justified by the stability at 30°C/75%RH (b) (4) (b) (4) plus accelerated, open-dish, and photostability studies.

Manufacturing process development is based on extensive prior knowledge (including the 3 previous products containing TAF) and risk assessment. Adequate studies have been conducted to define Proven Acceptable Range (PAR) for the process parameters to mitigate potential risks. Based on the study results proven acceptable ranges (PAR) for relevant process parameters for each unit operation have been adequately defined. (b) (4) (b) (4). The manufacturing process has been adequately described and controlled.

Evaluation of the manufacturing facilities supports approval as documented in the Facilities review, and the Overall Manufacturing Facility Status of "Approve" in Panorama.

The drug substance is highly soluble, and the drug product was formulated with (b) (4). The proposed dissolution method (Apparatus 2; 500 mL of pH 4.5 sodium acetate buffer; 75 rpm) was able to differentiate formulations (b) (4), and is acceptable for the purpose of quality control for this rapidly dissolving drug product. The acceptance criterion was revised to  $Q = \frac{(b) (4)}{(4)}\%$  in 15 minutes, which is supported by the dissolution data at release and on stability.

### C. Special Product Quality Labeling Recommendations

None

### D. Final Risk Assessment (see Attachment I)



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Miller

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## **R Regional Information**

### **Environmental Analysis**

A categorical exclusion from the requirement to prepare an environmental assessment is requested under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(b). This is also in accordance with the FDA Guidance for Industry – Environmental Assessment of Human Drug and Biologic Applications (July 1998, Revision 1), which is based on the final rule published on July 29, 1997 (62 FR 40569).

Tenofovir alafenamide (TAF) tablet is a single agent product consisting of one active pharmaceutical ingredient, tenofovir alafenamide (TAF) fumarate. The request for categorical exclusion is on the basis of a less than 1 part per billion (ppb) level of expected introduction concentration (EIC) for TAF at the point of entry into the aquatic environment.

The calculation of the individual EIC value for TAF into the aquatic environment as a result of the action is shown below, following the formula specified in the guidance document. In accordance with the guidance document, the calculation for TAF fumarate considers the Genvoya® (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fumarate) FDC (NDA 207561), F/TAF (emtricitabine and tenofovir alafenamide fumarate) FDC (NDA 208215), FTC/RPV/TAF (emtricitabine, ripilvirine and tenofovir alafenamide fumarate) FDC (NDA 208464) and TAF (tenofovir alafenamide fumarate) tablets (NDA 208464).

Tenofovir alafenamide fumarate

$$\text{EIC-Aquatic (ppb)} = A \times B \times C \times D$$

$$= \text{(b) (4)} \text{ kg/year} \times 1 / (1.214 \times 10^{11} \text{ liters/day}) \times (1 \text{ year} / 365 \text{ days}) \times (10^9 \text{ } \mu\text{g/kg}) = \text{(b) (4)}$$

Where

A = kg/year production of tenofovir alafenamide fumarate

B = 1/liters per day entering publicly owned treatment works (POTWs)

C = year/365 days

D =  $10^9 \mu\text{g/kg}$  (conversion factor)

The estimated annual production is based on the highest total quantity of TAF fumarate drug substances expected to be produced for use in the U.S. in any of the next five years for Genvoya, F/TAF FDC, FTC/RPV/TAF FDC, and the TAF tablets described in this NDA.

Because the estimated EIC for TAF fumarate is below 1 ppb, a categorical exclusion is requested. Gilead Sciences, Inc. claims that approval of this NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of Gilead’s knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

**Reviewer’s Assessment:** **Adequate**

Since the estimated EIC for TAF fumarate is below 1 ppb, the request for a categorical exclusion is acceptable. This approach for the claim for a categorical exclusion is as the same as NDA 208351 for Odefsey tablet containing 10 mg TFA, which is approved on March 1, 2016.

***Methods Verification Package***



Reviewer's Assessment: N/A

***Comparability Protocols***

Reviewer's Assessment: N/A

***{Assess if the protocol is scientifically sound and adequately designed to generate data that will support the acceptability of the drug substance between pre- and post-change material}***

***Post-Approval Commitments***

Reviewer's Assessment: N/A

***Lifecycle Management Considerations***

Reviewer's Assessment: N/A

***Primary Drug Product Reviewer Name and Date:***

***Yong Wang, Ph.D., August 24, 2016***

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

***Balajee Shanmugam, 9/7/2016***



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Shanmugam

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Wang

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**LABELING****NDA 208464****R Regional Information****1.14 Labeling**

(b) (4)

**Reviewer's Assessment:**

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Vemlidy Established name: Tenofovir alafenamide The established name is at least half as large as the type property name. The font size, prominence, and layout are acceptable.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	25 mg of TFA (equivalent to 28 mg of Tenofovir alafenamide fumarate)	Adequate
Route of administration (21.CFR 201.100(b)(3))	Not required for oral dosage form	Adequate
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)**	N/A	Adequate
Lot number per 21 CFR 201.18	The space for lot number is provided.	Adequate
Expiration date per 21 CFR 201.17	The space for expiration date is provided along with lot number.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" is displayed prominently on the main panel	Adequate
Storage	Store below 30 °C (86 °F) (see insert). Keep container tightly closed. Dispense only in original container. See package insert for dosage and administration.	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)	NDC- 61958-XXXX-x	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Yes, a bar code is provided.	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Gilead Sciences, Inc. Foster City, CA 94404	Adequate
Others	Note to pharmacist: Do not cover ALERT box with pharmacy label. ALERT: Find out about medicines that should NOT be taken with Vemlidy™	Adequate

\*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.

Reviewer’s Assessment: Adequate

*{Assess if immediate container label(s) comply with all regulatory requirements from a CMC perspective}*

#### ***Carton Labeling***

Gilead did not provide carton label. Refer to above Immediate Container Label.

Reviewer’s Assessment: N/A

#### **Package Insert**

##### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

Vemlidy™ (tenofovir alafenamide) tablets, for oral use

Initial U.S. Approval: 2015

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

Tablets: 25 mg of tenofovir alafenamide. (3)

Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
<b>Proprietary name and established name</b>	<b>Proprietary name:</b> Vemlidy  <b>Established name:</b> tenofovir alafenamide tablets	This section is acceptable since proprietary and established names are provided.  <b>Acceptable</b>
<b>Dosage form, route of administration</b>	<b>Dosage form(s):</b> Tablets  <b>Routes of administrations:</b> for oral use	Dosage forms and route of administration are provided.  <b>Acceptable</b>
<b>Controlled drug substance symbol (if applicable)</b>	NA	NA
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
<b>A concise summary of dosage forms and strengths</b>	Tablets: 25 mg of tenofovir alafenamide	The required information is available.  <b>Acceptable</b>

<b>Conclusion:</b>	<i>Adequate</i>
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**(b) "Full Prescribing Information" Section**

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

(b) (4) 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate).

(b) (4) yellow, round, film-coated, debossed with "GSI" on one side of the tablet and "25" on the other side of the tablet.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Dosage form(s): Tablets	Acceptable
Strengths: in metric system	Strengths: 25 mg	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The tablets are yellow, round, film-coated, debossed with "GSI" on one side of the tablet and "25" on the other side of the tablet.	Acceptable

**Reviewer's Assessment:                      Acceptable**

The content in section 3, DOSAGE FORMS AND STRENGTHS, is adequate.

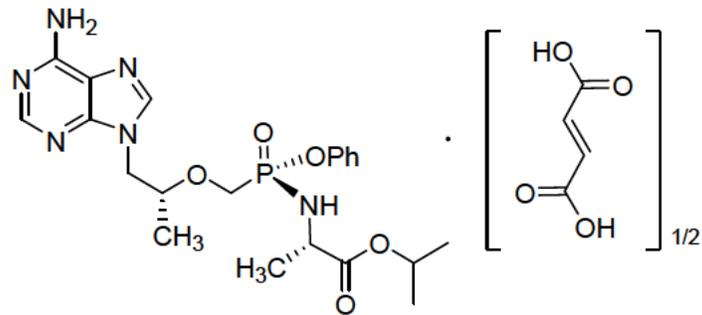
**#11: Description (21CFR 201.57(c)(12))**

Vemlidy is a tablet containing tenofovir alafenamide for oral administration. Tenofovir alafenamide is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

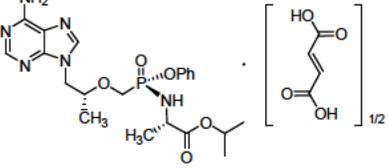
Each tablet contains 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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

It has an empirical formula of  $C_{21}H_{29}O_5N_6P \cdot \frac{1}{2}(C_4H_4O_4)$  and a formula weight of 534.50. It 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.

Item	Information Provided in NDA	Reviewer's Assessment
<b>Proprietary name and established name</b>	Proprietary name: Vemlidy Established name: Tenofovir alafenamide fumarate	<b>Acceptable</b>
<b>Dosage form and route of administration</b>	A tablet containing tenofovir alafenamide for oral administration	<b>Acceptable</b>
<b>Active moiety expression of strength with equivalence statement for salt (if applicable)</b>	Each tablet contains 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate)	<b>Acceptable</b>
<b>Inactive ingredient information (quantitative, if injectable 21CFR201.100(b)(5)(iii)), listed by USP/NF names.</b>	The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.	<b>Acceptable</b>
<b>Statement of being sterile (if applicable)</b>	N/A	N/A
<b>Pharmacological/ therapeutic class</b>	Tenofovir alafenamide is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.	<b>Acceptable</b>
<b>Chemical name, structural formula, molecular weight</b>	 <p>Chemical name: L -alanine, N-[(S)-[[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxy]phosphoryl]-, 1-methylethyl ester,</p>	<b>Acceptable</b>

	(2E)-2-butenedioate (2:1) Structural formula: $C_{21}H_{29}O_5N_6P \cdot \frac{1}{2}(C_4H_4O_4)$ Molecular weight: 534.50	
<b>If radioactive, statement of important nuclear characteristics.</b>	N/A	N/A
<b>Other important chemical or physical properties (such as pKa, solubility, or pH)</b>	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.	<b>Acceptable</b>

<b>Conclusion:</b>	<b>Acceptable</b>
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**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

Vemlidy tablets are yellow, round, film-coated, debossed with “GSI” on one side and “25” on the other side. Each bottle contains 30 tablets (NDC 61958-xxxx-x), a silica gel desiccant, 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.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Vemlidy tablets are yellow, round, film-coated, debossed with "GSI" on one side and "25" on the other side.	<p><b>Adequate</b></p> <p>The strength is not provided.</p> <p>"...containing 25 mg of TFA."</p> <p>Upon request, the applicant accepted the proposed change.</p>
Available units (e.g., bottles of 100 tablets)	Each bottle contains 30 tablets	<b>Acceptable</b>
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<p>NDC number:</p> <p>NDC 61958-XXXX-x</p> <p>Shape:</p> <p>Vemlidy tablets are yellow, round, film-coated, debossed with "GSI" on one side and "25" on the other side.</p>	<b>Acceptable</b>
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store below 30 °C (86 °F).	<b>Acceptable.</b>

**Manufacturer/distributor name listed at the end of PI, following Section #17**

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Gilead Sciences, Inc. Foster City, CA 94404	Acceptable

**Conclusion:*****Adequate***

The applicant should provide drug product strength information in the section of "How Supplied/Storage and Handling" per 21CFR 201.57(c)(17). 21CFR 201.57(c)(17). Therefore, the following IR is recommended to the applicant:

*Vemlidy tablets containing 25 mg of tenofovir alafenamide are yellow, round, film-coated, debossed with "GSI" on one side and "25" on the other side.*

The applicant accepted the proposed change shown above. Therefore, it is considered adequate.

***List of Deficiencies: None***

This proposed labeling and package insert are acceptable from the drug product perspective.

***Primary Labeling Reviewer Name and Date: Yong Wang Ph.D., 09/27/2016***

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

*Balajee Shanmugam, Ph.D., 09/27/2016*



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## PROCESS

**Product Background:** This TAF-alone immediate release tablet is indicated for treatment of chronic infection with the Hepatitis B virus in adults.

**NDA/ANDA:** NDA 208464

**Drug Product Name / Strength:** Tenofovir Alafenamide /25 mg

**Route of Administration:** Oral

**Applicant Name:** Gilead

### ***Review Summary:***

The manufacturing process for the TAF tablets is a (b) (4). This is the 4<sup>th</sup> product developed by the applicant that contains TAF fumarate. Quality assurance of other products from this applicant has been generally high. Manufacturing process development is based on extensive prior knowledge and risk assessment. Adequate studies have been conducted to define Proven Acceptable Range (PAR) for the process parameters to mitigate potential risks. Manufacturing process has been adequately described and controlled.

This application is recommended for approval from the process perspective.

**List Submissions being reviewed (table):** Original (dated 1/11/2016) and response (dated 8/9/2016)

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Concise Description Outstanding Issues Remaining:** N/A

## **P.3 Manufacture**

### ***Batch Formula***

The batch size for TAF tablets is (b) (4) kg, corresponding to approximately (b) (4) tablets, (b) (4). The manufacturing formula for the commercial batch size is given in [Table 2](#).

**Table 2. Batch Formula for TAF Tablets**

Components	Quality Standard	w/w (%)	Quantity per
Tenofovir Alafenamide Fumarate <sup>a</sup>	In-house		(b) (4)
Lactose Monohydrate	NF, Ph. Eur.		(b) (4)
Microcrystalline Cellulose	NF, Ph. Eur.		(b) (4)
Croscarmellose Sodium	NF, Ph. Eur.		(b) (4)
Magnesium Stearate	NF, Ph. Eur.		(b) (4)
Total Tablet Core Weight	--		(b) (4)

**Film-Coat**

(b) (4)	Yellow	(b) (4)	In-house	(b) (4)
(b) (4)			USP, Ph. Eur.	--

- a (b) (4)
- b (b) (4) Yellow (b) (4) contains (b) (4) Polyvinyl Alcohol (USP/Ph. Eur.), (b) (4) Titanium Dioxide (USP/Ph. Eur.), (b) (4) PEG (b) (4) (NF/Ph. Eur.), (b) (4) Talc (USP/Ph. Eur.) and (b) (4) Iron Oxide Yellow (NF)
- c (b) (4)
- d (b) (4)

**Reviewer's Assessment: Adequate**

The batch formula accurately reflects the proposed composition.

**Commercial Process Flow Diagram**

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**FACILITIES**

**Product Background:** Treatment of chronic hepatitis B infection

**NDA/ANDA:** NDA 208464/000

**Drug Product Name/Strength:** VEMLIDY™ (Tenofovir Alafenamide Fumerate) 25mg Tablet

**Route of Administration:** Oral

**Applicant Name:** Gilead Sciences Inc.

**Review Summary:** Adequate

**List Submissions being reviewed (table):**

Submission(s) Reviewed	Date Received
Submission amendment (Clinical/Response to IR)	08-AUG-2016
Submission amendment (Quality/Response to IR)	05-AUG-2016
Submission amendment (Clinical/Response to IR)	25-JUL-2016
Submission amendment (Labeling)	07-JUL-2016
Submission amendment (Clinical/Response to IR)	20-JUN-2016
Submission amendment (Clinical/Response to IR)	10-JUN-2016
Submission amendment (Quality/Response to IR)	08-JUN-2016
Submission amendment (Clinical/Response to IR)	20-MAY-2016
Submission amendment (Clinical/Response to IR)	09-MAY-2016
Submission amendment (Quality/Response to IR)	03-MAY-2016
Submission amendment (Clinical/Response to IR)	27-APR-2016
Submission amendment (Clinical/Response to IR)	21-APR-2016
Submission amendment (Clinical/Response to IR)	14-APR-2016
Submission amendment (Clinical/Response to IR)	07-APR-2016
Submission amendment (Clinical/Response to IR)	29-MAR-2016
Submission amendment (Quality/Response to IR)	25-MAR-2016
Submission amendment (Clinical/Response to IR)	18-MAR-2016
Submission amendment (Clinical/Response to IR)	15-MAR-2016
Submission amendment (Clinical/Response to IR)	26-FEB-2016
Submission amendment (Clinical/Response to IR)	24-FEB-2016
Submission amendment (Quality/Response to IR)	27-JAN-2016
Submission amendment (Proprietary Name)	12-JAN-2016
Original submission	11-JAN-2016

**Highlight Key Outstanding Issues from Last Cycle:** Not Applicable

**Concise Description Outstanding Issues Remaining:** None



***Lifecycle Management Considerations***

Not Applicable

***List of Deficiencies:*** Not Applicable

***Primary Facilities Reviewer Name and Date:***

Approve.

Frank Wackes, 09SEP2016

Consumer Safety Officer, OPQ/OPF/DIA/IABII

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

I support this approval recommendation.

Christina Capacci-Daniel, PhD – 09Sept2016

Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII



Christina  
Capacci-Daniel

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**BIOPHARMACEUTICS**

**Product Background:**

**NDA/ANDA: NDA 208464**

**Drug Product Name / Strength: Tenofovir Alafenamide Tablet (TAF)/ 25 mg**

**Route of Administration: Oral**

**Applicant Name: Gilead Sciences, Inc.**

***Review Summary:***

Tenofovir Alafenamide (TAF) 25mg tablet is indicated for the treatment of chronic hepatitis B. The drug substance is highly soluble and the drug product is formulated for immediate release. The proposed in vitro dissolution test is adequate for quality control. The selection of the dissolution conditions (e.g., medium, rotation speed, etc.) was adequately justified. The revised dissolution acceptance criterion was supported by the dissolution data provided, and is acceptable.

From a Biopharmaceutics perspective, NDA 208464 for Tenofovir Alafenamide 25 mg is recommended for APPROVAL.

The following regulatory dissolution method and revised acceptance criterion are acceptable:

Apparatus	USP Apparatus 2 (paddle)
Volume	500 mL
Paddle speed	75 rpm
Medium pH	4.5
Buffer and concentration	50 mM sodium acetate buffer
Temperature	37.0±0.5 °C
Acceptance criterion	Q= <sup>(b)</sup> <sub>(4)</sub> % in 15 min

**List Submissions being reviewed (table):**

eCTD sequence #	Received date	Document
0000	01/11/2016	New NDA
0013	05/03/2016	Quality/ Response to Information Request
0016	06/08/2016	Quality/ Response to Information Request

**Highlight Key Outstanding Issues from Last Cycle:** None.

**Concise Description Outstanding Issues Remaining:** None.

**BCS Designation**

**Reviewer’s Assessment:**

The drug substance Tenofovir Alafenamide has not been evaluated by the FDA BCS committee.

**Solubility:** The solubility of TAF fumarate in various organic solvents and in aqueous media at 20 °C is shown in Table 1 and 2 respectively.

Table 1. Solubility of TAF fumarate in selected solvents

Solvent	Solubility <sup>a</sup> (mg/mL)	USP/Ph. Eur. Solubility Description
Methanol	189	Freely soluble
Ethanol	69.6	Soluble
Isopropanol	27.7	Sparingly soluble
Acetone	9.16	Slightly soluble
Acetonitrile	2.30	Slightly soluble
Toluene	0.14	Very slightly soluble

a Determined at about 20 °C

Table 2. Solubility of TAF fumarate in Aqueous Media

Aqueous Media	Solubility <sup>a</sup> (mg/mL)	USP/Ph. Eur. Solubility Description
Water, pH 2.0 (HCl)	85.4	Soluble
Water, final pH 3.8	21.7	Sparingly soluble
Water, pH 4.5 (20 mM acetate buffer)	8.73	Slightly soluble
Water, pH 6.8 (50 mM phosphate buffer)	4.70	Slightly soluble
Water, pH 8.0 (50 mM phosphate buffer)	4.86	Slightly soluble

a Determined at about 20 °C

The 25 mg TAF dose is soluble in less than 7 mL of aqueous media across the physiological pH range. Therefore, according to the BCS guidance, TAF is a highly soluble drug. The Applicant noted that TAF is a BCS class 3 compound.

**Permeability:** The Applicant noted that the permeability of TAF is low, but no supportive data are provided.

**Dissolution:** See the section below.

*Dissolution Method and Acceptance Criteria*

The proposed dissolution method is summarized in Table 3.

Table 3. Dissolution method parameters

Apparatus	USP Apparatus 2 (paddle)
Volume	500 mL
Paddle speed	75 rpm
Medium pH	4.5
Buffer and concentration	50 mM sodium acetate buffer
Temperature	37.0±0.5 °C

(b) (4)

### Stability data

The Applicant provided the complete dissolution data for 4 stability batches under long-term storage condition (25 °C/60% RH). There are more than 95% of drug dissolved at 15-min (the revised specification time point) in storage time up to 24 months. All stability batches conform to the revised dissolution acceptance criterion.

### **Reviewer's Assessment:**

- The drug substance is highly soluble, and the drug product was formulated with (b) (4).
- Initially, the full development report for the dissolution method was not located and the following IR comment was sent to the Applicant on April 19, 2016.

*Investigate the effect of rotation speed on the dissolution profile of TAF tablets. Provide the full profile dissolution data (mean, individual, SD, figure, n = 12) for TAF tablets using the speeds of 50 rpm and 60 rpm in the proposed medium.*

The IR response was received on May 3, 2016, which provided adequate justifications for the proposed dissolution test parameters, including selection of the pH of the medium, selection of apparatus and rotation speed. The method was adequately validated. The response was acceptable.

- The proposed dissolution method was able to differentiate formulations (b) (4). Change in particle size of the drug substance does not impact the dissolution profile. Though the discriminating ability of the method was not adequately established, the method is acceptable for the purpose of quality control for this rapidly dissolving drug product.

- The Applicant initially proposed an acceptance criterion of “Q= (b) (4) % in (b) (4) min”, which is not supported by the dissolution data. The following IR comment was sent to the Applicant on May 25, 2016.

*The provided dissolution data do not support the proposed dissolution acceptance criterion of Q = (b) (4) % at (b) (4) minutes and it is not acceptable. Implement the following dissolution acceptance criterion for your proposed drug product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.*

$$Q = (b) (4) \% \text{ at } 15 \text{ min}$$

The Response was received on June 8, 2016. The Applicant accepted the recommended acceptance criterion and revised the specification tables accordingly. The long-term stability data conform to the revised acceptance criterion.

- The following regulatory dissolution method and acceptance criterion are acceptable:

Apparatus	USP Apparatus 2 (paddle)
Volume	500 mL
Paddle speed	75 rpm
Medium pH	4.5
Buffer and concentration	50 mM sodium acetate buffer
Temperature	37 (b) (4) 0.5 °C
Acceptance criterion	Q (b) (4) % in 15 min

- OPQ Risk Mitigation Dashboard- In vitro dissolution:

In-Vitro Dissolution		
<b>Initial Risk</b>	Low	
<b>Comment</b>	The drug substance is highly soluble and the drug product is formulated for immediate release	
	<b>Mitigation</b>	<b>Comment</b>
<b>Design</b>	Formulation design to achieve rapid dissolution/disintegration (excipient includes (b) (4))	Refer to Drug Product Quality Review
<b>Process</b>		
<b>Measurement</b>	Dissolution acceptance criterion/a that assures consistent bioavailability of the drug product since the dissolution is rapid and not rate limiting for absorption	Refer to the section of <u>Dissolution Method and Acceptance Criterion</u>
	Dissolution testing method is well justified, characterized and understood (b) (4) (b) (4)	Refer to the section of <u>Dissolution Method and Acceptance Criterion</u>

***Bridging of Formulations***

**Reviewer's Assessment:**

The proposed commercial formulations are identical to formulations used in the pivotal bioequivalence studies, Phase 3 studies and in registration stability study.

***Primary Biopharmaceutics Reviewer Name and Date:***

Jing Li, Ph.D., 7/22/2016  
Biopharmaceutics Reviewer  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

I concur with Dr. Li's assessment and recommendation.  
Elsbeth Chikhale, Ph.D., 8/23/2016  
Acting Biopharmaceutics Lead  
Division of Biopharmaceutics  
Office of New Drug Products  
Office of Pharmaceutical Quality



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Jing  
Li

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## ATTACHMENT I: Final Risk Assessments

### OPQ Risk Mitigation Dashboard

<b>A/NDA:</b> 208464		
<b>Drug Product:</b> Vemlidy (tenofovir alafenamide tablet)		
<b>Dosage:</b> Tablet		
<b>Strength:</b> 25 mg		
<b>Applicant:</b> Gilead		
Physical Stability		
<b>Initial Risk</b>	Low	
<b>Comment</b>	Similar to Genvoya tablets with 10mg TAF	
	Mitigation	Comment
<b>Design</b>	(b) (4)	TAF has been approved before as 3 other tablets and its physical properties are well understood
	(b) (4)	
<b>Process</b>	(b) (4) process	
<b>Measurement</b>		
Chemical Stability		
<b>Initial Risk</b>	Medium	
<b>Comment</b>	The major degradation product (b) (4)	
	Mitigation	Comment
<b>Design</b>	(b) (4)	
		Desiccant (b) (4) is used in container closure system
<b>Process</b>		
<b>Measurement</b>	Real time stability data demonstrates drug product is stable through granted shelf-life and well within the margin of specification limits	
In-Vitro Dissolution		
<b>Initial Risk</b>	Low	
<b>Comment</b>	the drug substance is highly soluble and the drug product is formulated for immediate release	
	Mitigation	Comment
<b>Design</b>	(b) (4)	
<b>Process</b>		

	(b) (4)	
<b>Measurement</b>	Dissolution acceptance criterion/a that assures consistent bioavailability of the drug product since the dissolution is rapid and not rate limiting for absorption)	
	Dissolution testing methods are well justified, characterized and understood (e.g. use of (b) (4)	
<b>Content Uniformity</b>		
<b>Initial Risk</b>	Medium	
<b>Comment</b>	Concern is medium because of (b) (4)	
<b>Process/Facility</b>	<b>Mitigation</b>	<b>Comment</b>
<b>Unit Operation</b>	(b) (4)	
<b>Process Design</b>		
<b>Parameters</b>		
<b>Input MA</b>	(b) (4)	(b) (4)
<b>Output QA</b>		
<b>Scale-Up</b>	(b) (4)	1 commercial scale batch included in NDA
	<b>Mitigation</b>	<b>Comment</b>
<b>Measurement (Routine)</b>		
<b>Additional CQA</b>		
<b>Attribute</b>	<b>Rationale</b>	<b>Risk Mitigation</b>
(b) (4)		(b) (4)
		(b) (4)

Note: text in blue are aspects that are relevant to this NDA, and could be considered for addition to future updates of the Risk-Mitigation Dashboard tool.

## ATTACHMENT II: List of Deficiencies for Complete Response

Responses have been received to all Information Requests, and there are no remaining deficiencies from the Product Quality perspective.

**OVERALL ASSESSMENT AND SIGNATURES:**

From the Product Quality perspective NDA 208464 is recommended for Approval.

Stephen Miller, Ph.D.; CMC-Lead and ATL for NDA 208464



Stephen  
Miller

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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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JONATHAN T DOW  
11/18/2016