CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207561Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
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Date: July 9, 2015

To: George Lunn, CMC Reviewer, CDER/OPQ/ONDQA
Jeff Medwid, CMC Reviewer, CDER/OPQ/ONDQA
Stephen Miller, CMC Lead
Youbang Liu, ONDQA Methods Validation Project Manager

From: Jingyue Yang, Ph.D., Chemist, CDER/OPQ/OTR/DPA
Jeffrey Woodruff, Chemist, CDER/OPQ/OTR/DPA

Through: David Keire, Ph.D., Lab Chief, Branch I

Subject: Method Verification of NDA 207561: Genvoya Tablets (150 mg Cobicistat, 200 mg Emtricitabine, 10 mg Tenofovir Alafenamide, 150 mg Elvitegravin)

The following methods were verified and found acceptable for quality control and regulatory purposes.

1) **TM-227.00** Identification, Assay, and Impurity Content of Tenofovir Alafenamide Fumatate Drug Substance by HPLC
2) **TM-232.00** Identification, and Content Uniformity of E/C/F/TAF Tablets by HPLC
3) **TM-233.00** Dissolution of E/C/F/TAF Tablets
4) **TM-234.00** Determination of Specific FTC and TAF Degradation Products in E/C/F/TAF Tablets by UPLC

The following method was verified and found acceptable for quality control and regulatory purposes with comments.

1) **TM-231.01** Identification, Assay, and Degradation Products of E/C/F/TAF Tablets by UPLC

Issue: (b) (4)

Comments for TM-231

- TM-231: (b) (4)

The following methods were reviewed and found to be acceptable:

1) **TM-230** Elemental Impurity Analysis of Tenofovir Alafenamide Fumarate by ICP/MS
2) **STM-0049.01** Clarity of Solution Determination of Tenofovir Alafenamide (TAF) Fumarate Drug Substance
3) **TM-229** Determination of Identity and (b) (4) Content in Tenofovir Alafenamide Fumarate Drug Substance by HPLC
4) **TM-228** Residual Solvent and (b) (4) Content of Tenofovir Alafenamide
5) **TM-236** (b) (4) Content in Tenofovir Alafenamide Fumarate by HPLC-MS

Link to analyst's work sheets and data: http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880aeccce

Summary of Analysis

1) **TM-232.00** Identification, and Content Uniformity of E/C/F/TAF Tablets by HPLC

The specification is met.

Content Uniformity		
	AV	Pass/Fail
FTC	(b) (4)	Pass
TAF		Pass
COBI		Pass
EVG		Pass
Limit: AV NMT (b) (4)		

2) **TM-233.00** Dissolution of E/C/F/TAF Tablets

The specification is met (each tablet % dissolved NLT (b) (4)).

	% Dissolved							
API	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	S.D.
FTC	(b) (4)							
TAF								
COBI								
EVG								

3) **TM-227.00** Identification, Assay, and Impurity Content of Tenofovir Alafenamide Fumatate Drug Substance by HPLC

The specifications are all met.

Test	Specification	Results
Identification	The retention time of TAF peak is consistent with that of reference standard	Conforms
Assay	NLT (b) (4) and NMT (b) (4)%	(b) (4)%
Impurity Content		
Total	NMT (b) (4)%	(b) (4)%
(b) (4)	NMT %	%
	NMT %	%
	NMT %	(b) (4)%
	NMT %	%
	NMT %	%
	NMT %	(b) (4)%
	NMT %	%
	NMT %	%
	NMT %	not detected
	Not found	not detected
Unspecified impurity	NMT (b) (4)%	(b) (4)%

Comments for TM-227.00

- The formula to calculate the sample concentration in TM-227 is not correct because [redacted] (according to TM-229.00 and specification). The correct formula should be:

Sample concentration = [redacted]

However, the sample concentration calculated from the above formula does not differ significantly from that calculated from the incorrect formula in the method. The results should not be affected.

- It is suggested the definition of RRF (relative response factor) be clarified in the method to avoid confusion on calculation. RRF of an impurity is commonly defined as the ratio of impurity response factor to API response factor, but RRF is used in the method as the reverse order without definition or explanation.

4) **TM-231.01** Identification, Assay, and Degradation Products of E/C/F/TAF Tablets by UPLC; **TM-234.00** Determination of Specific FTC and TAF Degradation Products in E/C/F/TAF Tablets by UPLC

Assay

API	Specification (release)	Results	Evaluation
EVG	[redacted]%	103.9%	Pass
COBI	[redacted]%	102.5%	Pass
FTC	[redacted]%	100.3%	Pass
TAF	[redacted]%	104.1%	Pass

Degradation Products

Cobicistat (COBI) Degradation Products

Degradants	RT	RRT	Amount	Determined by	Specification (release)	Evaluation
[redacted]			[redacted]	TM-231	NMT [redacted]%	Pass
				TM-231	NMT [redacted]%	Pass
				TM-231	NMT [redacted]%	Pass
				TM-231	NMT [redacted]%	Pass
				TM-231	NMT [redacted]%	Pass
				TM-231	NMT [redacted]%	Pass
				TM-231	Not found	N/A
Unspecified			[redacted]	TM-231	NMT [redacted]%	Pass
Total degradants			[redacted]% *		NMT [redacted]%	Pass

[redacted]

Tenofovir Alafenamide (TAF) Degradation Products

Degradants	RT	RRT	Amount	Determined by	Specification (release)	Evaluation
[redacted]			(b) (4)	TM-231	NMT (b) (4) %	
				TM-231	NMT %	
				TM-234	NMT %	Pass
				TM-234	NMT %	
				TM-234	NMT %	
Unspecified (b) (4)			%	TM-231	NMT (b) (4) %	Pass
Total degradants			(b) (4) %		NMT (b) (4) %	Pass

[redacted] (b) (4)

Elvitegravir (EVG) Degradation Products

Degradants	Amount	Determined by	Specification (release)	Evaluation
Unspecified degradants	(b) (4)	TM-231	NMT (b) (4) %	Pass
Total degradants	(b) (4) %		NMT %	Pass

(b) (4)

Emtricitabine (FTC) Degradation Products

Degradants	RT	RRT	Amount	Determined by	Specification (release)	Evaluation
[redacted]			(b) (4)	TM-231	Not found	N/A
				TM-231	Not found	N/A
				TM-231	Not found	N/A
				TM-234	Not found	N/A
				TM-231	NMT (b) (4) %	Pass
Total degradants			(b) (4) %		NMT (b) (4) %	Pass

(b) (4) [redacted]

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/s/

LAURA POGUE
07/09/2015

DAVID A KEIRE
07/09/2015

Recommendation: Approval

NDA 207561
Review #1
July 9, 2015

Drug Name/Dosage Form	Genvoya Tablets Elvitegravir, Cobicistat, Emtricitabine and Tenofovir Alafenamide (E/C/F/TAF)
Strength	150mg / 150mg / 200mg / 10mg
Route of Administration	Fixed-Dose Combination Tablet
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	NA

Submission(s) Reviewed	Document Date
Original	05-Nov-2014
Amendment	06-Feb-2015
Amendment	18-Feb-2015
Amendment	10-Mar-2015
Amendment	13-Apr-2015
Amendment	17-Apr-2015
Amendment	05-Jun-2015
Amendment (stability update)	12-Jun-2015
Amendment	02-Jul-2015
Amendment (container labels)	07-Jul-2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeff Medwid	ONDP/DNDAPI/Branch II
Drug Product	George Lunn	ONDP/DNDP-I/Branch III
Process	Lin Qi	OPF/DPAIII/PABVII
Microbiology	Jessica Cole	OPF/DMA/Branch III
Facility	Krishna Ghosh	OPF/DIA/IABIII
Biopharmaceutics	Salaheldin Hamed	ONDP/DB/Branch III
Project/Business Process Manager	Navi Bhandari	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Steve Miller	ONDP/DNDP-I/Branch III
Laboratory (OTR)	Akhtar Siddiqui	OTR/DPQR/PQBII
ORA Lead	Sharon Thoma	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Covered by DP review	

Table of Contents

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505b1

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
25188	Type II	Gilead	Cobicistat on Silicon Dioxide(drug substance)	Adequate	April 14, 2015	Reviewed By Yong Wang
25187	Type II	Gilead	Elvitegravir drug substance info	Adequate	July 2, 2015	Reviewed by Jeffrey Medwid
[redacted]				N/A		
				N/A		
				N/A		
				N/A		
				N/A		
				N/A		
				N/A		
				N/A		
				N/A		
				N/A		

(b) (4)

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[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 111007		This product during IND development
NDA for Emtricitabine (FTC)	NDA 21-772	Emtricitabine (FTC) drug substance information

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				
Methods Validation	Adequate	The report from the FDA laboratory indicates that the methods are suitable for regulatory purposes.	08-Jul-2015	David Keire

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 207561 is recommended for approval from the Product Quality perspective. CMC-related labeling recommendations have been provided to the OND PM, for consideration during final labeling.

1. Summary of Complete Response issues Not Applicable
2. Action letter language, related to critical issues such as expiration date
   - "We also acknowledge receipt of information related to Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) tablets 150 mg/150 mg/200mg/10mg for your Gilead Access Program that was included in this application."
   - "An expiration dating period of 24 months is approved for Genvoya tablets when packaged and stored as described in the attached labeling."
3. Benefit/Risk Considerations
   Evaluation of the quality aspects of Genvoya tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

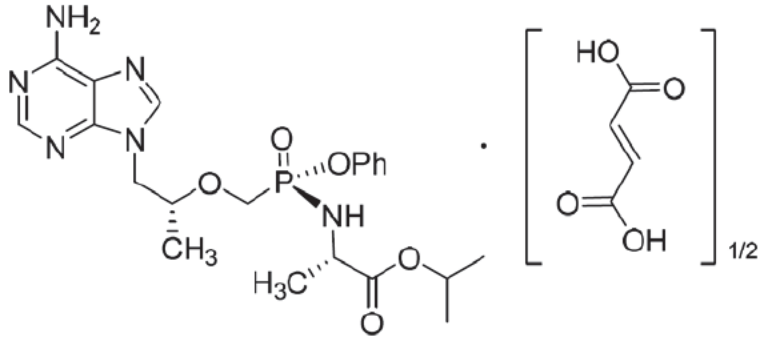
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

II. Summary of Quality Assessments

A. Drug Substance [Tenofovir Alafenamide Fumarate] Quality Summary

Tenofovir alafenamide fumarate is a new prodrug of tenofovir. It is considered to be a New Molecular Entity because it differs from the previously approved prodrug, tenofovir disoproxil fumarate, by features such as the phosphonamide linkage that are not esters.

1. Chemical Name or IUPAC Name/Structure
   USAN Name: "Tenofovir Alafenamide Fumarate"
   (1) l-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2-butenedioate (2:1); (2) 1-Methylethyl N-[(S)-{[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl}phenoxyphosphinoyl]-l-alaninate, (2E)-2-butenedioate.



2. Properties/CQAs Relevant to Drug Product Quality
   a. The solid state form (2:1 stoichiometry) was selected over the "monofumarate" (1:1 stoichiometry) which was used in Phase I. Based on current scientific knowledge, the drug substance may be either a salt (if protons are transferred from fumaric acid to TAF) or a co-crystal (if the protons remain on the fumaric acid).
   b. To ensure a consistent particle size for all future batches of drug substance going into the drug product, Gilead has agreed to incorporate the particle size acceptance limit of NMT (b) (4) µm at d_{90} into the final drug substance specification.
   c. Information Relevant to Impurity Control: Maximum Daily Dose of TAF fumarate is 10 mg/day for this indication. Acceptable Intake of Mutagenic Impurities: (b) (4) ug/day at 10 mg/day maximum dose = (b) (4)% for TAF fumarate. (b) (4)
3. List of starting materials: (b) (4)
4. Suppliers of starting materials (site): Starting materials and their specifications were selected so that additional vendors and their methods of manufacturing the starting materials could be adopted under the applicant's pharmaceutical quality system.
5. Summary of Synthesis: (b) (4)
6. Process
   a. Sterilization processes of the sterile bulk, as applicable NA
   b. Critical equipment: None
7. Summary of Drug Substance Controls: The TAF fumarate specification includes all of the key drug substance tests including Identity, Clarity of Solution, Water Content (NMT (b) (4)%), Assay (b) (4), Impurity Content (NMT (b) (4)% total Impurities with control of 9 specific impurities), Impurity content by GC (NMT (b) (4)% (b) (4) and NMT (b) (4)% Unspecified impurities), (b) (4) Content (NMT (b) (4)%), (b) (4) Content, Elemental Impurities, Residual Solvents, Melting Point and Particle Size.

8. Retest Period & Storage Conditions: 24 months when stored at 5°C

A. Drug Substance [Elvitegravir] Quality Summary

See DMF 25187 and detailed review notes, below

A. Drug Substance [Cobicistat] Quality Summary

See DMF 25188 and detailed review notes, below

A. Drug Substance [Emtricitabine] Quality Summary

See NDA 21752 and detailed review notes, below

B. Drug Product Quality Summary for Genvoya Tablets

The drug product consists of green capsule-shaped film-coated tablets packaged 30 count in white HDPE bottles containing silica gel desiccant and a polyester coil and capped with child-resistant closures. White tablets for an access program are also described. The only differences are in the (b) (4). The current formulation is closely related to Stribild tablets which contain elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate. (b) (4)

The excipients are compendial except for the film coat which is made from compendial components. There are no novel excipients.

All analytical methods are described in reasonable detail and have been validated. A Methods Validation package is provided and validation by an FDA laboratory was been requested. The FDA laboratory indicates that the methods are suitable for regulatory purposes. Satisfactory batch analyses are provided for 20 batches ranging from (b) (4) kg.

Eighteen months of stability data obtained at 25°C/60% RH and 30°C/75% RH and 6 months of data obtained at 40°C/75% RH are provided for 3 batches and lesser amounts of data are provided for a further 5 batches. (b) (4) These results include statistical analysis, and support both the expiration dating period and storage statement listed below.

1. Strength
   Elvitegravir, cobicistat, emtriticitabine and tenofovir alafenamide; 150mg / 150mg / 200mg / 10mg (as 11.2 mg tenofovir alafenamide fumarate)
2. Description/Commercial Image
   US Image: capsule-shaped green film-coated tablets debossed with "GSI" on one side and "510" on the other side.

Access Image: capsule-shaped white film-coated tablets debossed with "GSI" on one side and "A510" on the other side.

3. Summary of Product Design: (b) (4) immediate-release tablet
4. List of Excipients: See review notes, below
5. Process Selection (Unit Operations Summary)
   Genvoya tablets are manufactured (b) (4)

   As amended, the applicant made the following commitments, related to the manufacturing process, (b) (4)
   - Throughout development, (b) (4) Gilead commits to continue using the same grades of hydroxypropyl cellulose, lactose monohydrate, and microcrystalline cellulose during commercial manufacturing of Genvoya tablets.
   - (b) (4) testing will be conducted on the process validation batches. Samples used for testing will be collected using a stratified sampling scheme (n=20 locations).

   In conclusion, the applicant provided sufficient data (16 clinical and stability batches) to demonstrate the consistency of the proposed commercial manufacturing process at the proposed commercial scale.
   a. Sterilization processes of the drug product, as applicable: NA
   b. Critical equipment: (b) (4)
6. Summary of Drug Product Controls
   a. The DP specification contains tests for appearance, identity, (b) (4), assay, degradants, dose uniformity, dissolution, and microbial limits and is, as amended, acceptable.
   b. The microbiological controls include compendial release and annual stability testing according to USP<61> and <62>. The limits are 10^3 total aerobic microbial count, 10^2 total yeast and molds, and the absence of Escherichia coli.
7. Container Closure Both US and Access versions are HDPE bottles of 30 containing desiccant, polyester filler, induction seal and CR cap.
8. Expiration Date & Storage Conditions 24 months with the storage statement of "Store below 30°C"
9. List of co-packaged components None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Genvoya Tablets
Non Proprietary Name of the Drug Product	Elvitegravir, cobicistat, emtriticitabine and tenofovir alafenamide
Non Proprietary Name of the Drug Substance	Elvitegravir; cobicistat; emtriticitabine; tenofovir alafenamide fumarate
Proposed Indication(s) including Intended Patient Population	Treatment of HIV infection
Duration of Treatment	Chronic dosing until resistance develops
Maximum Daily Dose	1 tablet per day
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance: Elvitegravir (Class II; solubility less than 0.001 mg/mL), Cobicistat (Class II; low solubility at high pH), TAF fumarate (Class III; solubility 4 mg/mL to 50 mg/mL), and Emtricitabine (Class I)
   - Drug Product: No BCS information was submitted for drug product

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A (a fixed-dose combination)
   - PK studies: N/A (no formulation bridging was necessary during clinical development)
   - IVIVC: N/A (no IVIVC data were submitted)

E. Novel Approaches None

F. Any Special Product Quality Labeling Recommendations None

G. Process/Facility Quality Summary

See detailed Risk Assessment Tables for Drug Substance and Drug Product Facilities in review notes, below.

H. Life Cycle Knowledge Information

a) TAF Fumarate Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Initial Risk Ranking ***	**Justification**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations & Comments****
Process Impurities	L		Appropriate starting materials; controls on mutagenic imps (any controlled via each unspecified?)	Acceptable (L)	
Stability / degradants	M		(b) (4) storage of DS	Acceptable (L)	
Solid-State form	L	(b) (4)	Specification includes melting point (specific to this solid-state form) and limits on water content	Acceptable (L)	
PSD	M		Monitoring is now included on DS spec	Acceptable (L)	See Content Uniformity and Dissol in DP Risk Table

b) Genvoya Tablets

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations & Comments****
Assay, Stability	(b) (4)	L		Acceptable (L)	Product is reasonably stable. (b) (4)
Physical stability (solid state)	(b) (4)	M	(b) (4)	Acceptable (L)	
Content uniformity	(b) (4)	M	Batches with d_{90} of (b) (4) µm demonstrated acceptable dissolution and uniformity. TAF fumarate d_{90} now in DS specification	Acceptable (L)	
Microbial limits	Compendial Microbial Enumeration	L	Control occurs through compendial release testing	Acceptable (L)	If reduced microbial testing is proposed in the future then additional information may be

	occurs at release and on stability				needed on in-process controls to limit microbial contamination/proliferation
Dissolution – BCS Class II & IV	(b) (4)	M	(b) (4)	Acceptable (L)	(b) (4)
Dissolution – BCS Class I & III	TAF fumarate and emtricitabine are highly soluble	L		Acceptable (L)	
(b) (4)		M	(b) (4)	Acceptable (L)	Related to CQA for Degradants (below)

Drug Product Impurity Control	Complex due to four APIs (b) (4) [redacted]	M	(b) (4) [redacted] ee additional discussion in "Assay, Stability" row, above	Acceptable (M)	(b) (4) [redacted]

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:

This NDA is recommended for approval 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: 2015.07.09 19:11:37 -04'00'

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

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S Tenofovir Alafenamide Fumarate Drug Substance

2.3.S.1 General Information

1. GENERAL INFORMATION [TENOFOVIR ALAFENAMIDE FUMARATE]

Information on the nomenclature of the drug substance, tenofovir alafenamide (TAF) fumarate, is provided below.

IUPAC: Propan-2-yl *N*-[(*S*)-({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl] oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2*E*)-but-2-enedioate (2:1)

CAS: 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)

Synonym: TAF fumarate

CAS Registry Number: 1392275-56-7

INN: Not available

USAN: Tenofovir alafenamide fumarate

Gilead Code Number: GS-7340-03
Additionally, information on the nomenclature of the free base of the drug substance, i.e. tenofovir alafenamide, is provided below.

IUPAC: Propan-2-yl (2S)-2-[[1-(6-aminopurin-9-yl)propan-2-yloxymethylphenoxyphosphoryl] amino]propanoate

CAS: Propan-2-yl (2S)-2-[[1-(6-aminopurin-9-yl)propan-2-yloxymethylphenoxyphosphoryl] amino]propanoate

Synonym: TAF

CAS Registry Number: 379270-37-8
INN: Tenofovir alafenamide

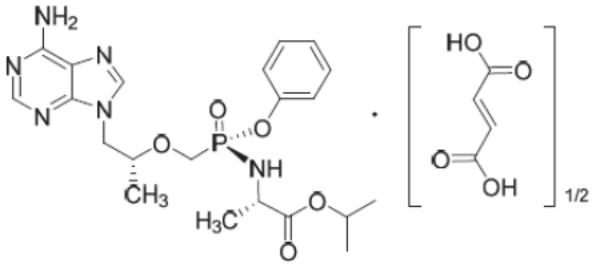
USAN: Tenofovir alafenamide

Gilead Code Number: GS-7340

2. STRUCTURE [TENOFOVIR ALAFENAMIDE FUMARATE]

The empirical formula, the relative formula weight, and the structural formula of the drug substance TAF fumarate are provided below.

Empirical Formula: $C_{23}H_{31}O_7N_6P$
Formula Weight: 534.5
Structural Formula:



Additionally, the molecular formula and relative molecular weight of the free base of the drug substance, tenofovir alafenamide are provided below.
Molecular Formula: $C_{21}H_{29}O_5N_6P$
Molecular Weight: 476.5

3. GENERAL PROPERTIES [TENOFOVIR ALAFENAMIDE FUMARATE]

The physical and chemical characteristics of TAF fumarate are provided below.

Appearance: TAF fumarate is a white to off-white or tan powder.

Stereochemistry: TAF fumarate has three chiral centers. The chiral center at the propyloxy side chain is in the *R*-configuration. The absolute stereoconfiguration of the carbonylethylamino substituent is derived from the amino acid L-alanine, which has the *S*-configuration at the alpha-carbon. The remaining stereocenter is located at the phosphorus atom and is in the *S* configuration.

Polymorphism: (b) (4)

Melting Onset : Approximately 132 °C

pKa: 3.96

Partition Coefficient: Log P is 1.6 (1-octanol/phosphate buffer pH 7).

(b) (4)

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

Table 1. Solubility of TAF Fumarate in Selected Solvents

Solvent	Solubility[a] (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[a] (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

Reviewer's Assessment:

All information provided for the General Information, properties, and structure of TAF is adequately and accurately provided.

2.3.S.2 Manufacture

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
This NDA is recommended for approval from the CMC drug substance perspective. All CMC issues concerning the drug substance have been satisfactorily resolved. The manufacturing process and controls, specifications and analytical methods for all four API's (**Elvitegravir, Cobicistat, Emtricitabine and Tenofovir Alafenamide Fumarate (E/C/F/TAF)** are appropriate. The container-closure systems and labeling are appropriate.

Jeffrey B. Medwid, PhD., Senior Review Chemist, Branch II, Division of New Drug API. July 8, 2015

Supervisor Comments and Concurrence:

I concur with Dr. Medwid's conclusion on the acceptability of the drug substance information for Elvitegravir, Cobicistat, Emtricitabine and Tenofovir Alafenamide Fumarate (E/C/F/TAF).

Donna F. Christner,Ph.D., Acting Chief, Branch II, Division of New Drug API. July 8, 2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

(Include a summary of how the product design relates to the proposed patient population and the clinical indication. (e.g., rationale for the dosage selections, unique design features of the proposed drug product etc.).

2.3.P.1 Description and Composition of the Drug Product

7. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Information:

The drug product consists of green capsule-shaped film-coated tablets debossed with "GSI" on one side and "510" on the other. The tablets are 19 mm long and 8.5 mm wide. Tablets in the alternate trade dress are white and debossed with "GSI" on one side and "A510" on the other. The tablets are packaged 30 count in 100 mL white HDPE bottles containing 3 g of silica gel desiccant and a polyester coil. The bottles are capped with (b) (4) screw caps and an induction seal.

Component	Function	Amount	Percentage
(b) (4)			

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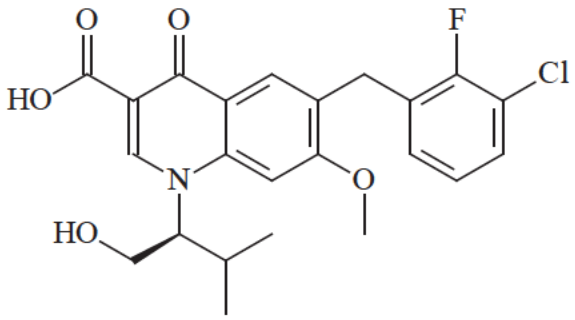
Reviewer's Assessment: Adequate. The tablet is complex with four drug substances but generally conventional. [redacted] (b) (4) All excipients and the components of the film coat are compendial.

2.3.P.2 Pharmaceutical Development

P.2.1.1 Drug Substance

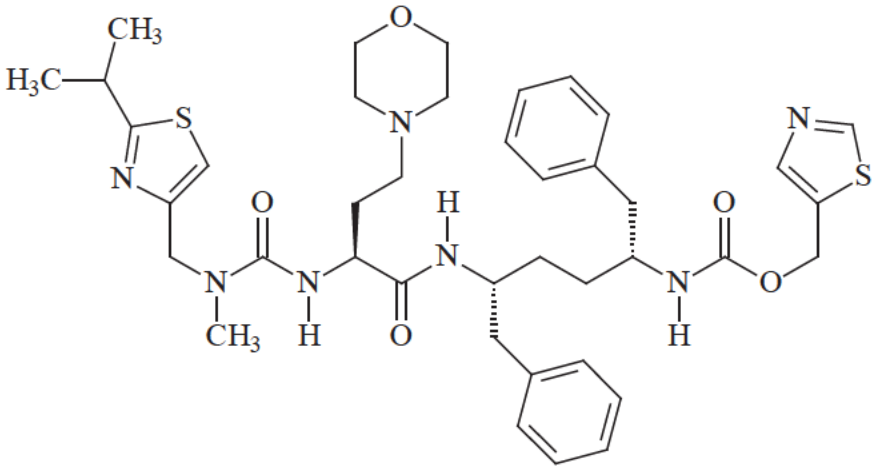
The drug substances are selected for reasons of clinical efficacy. See also drug substance reviews.

Elvitegravir



[redacted] (b) (4) Elvitegravir is BCS Class 2 with low solubility and high permeability.

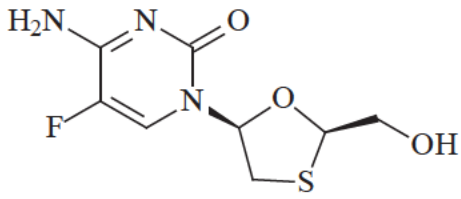
Cobicistat on Silicon Dioxide



(b) (4)

Cobicistat on silicon dioxide is BCS Class 2 with low solubility and high permeability.

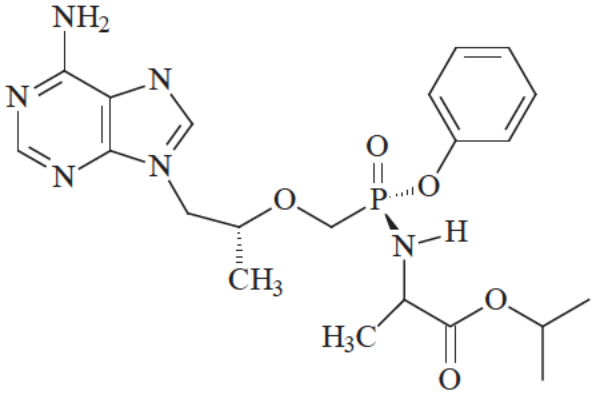
Emtricitabine (FTC)



(b) (4)

Emtricitabine is BCS Class 1 with high solubility and high permeability.

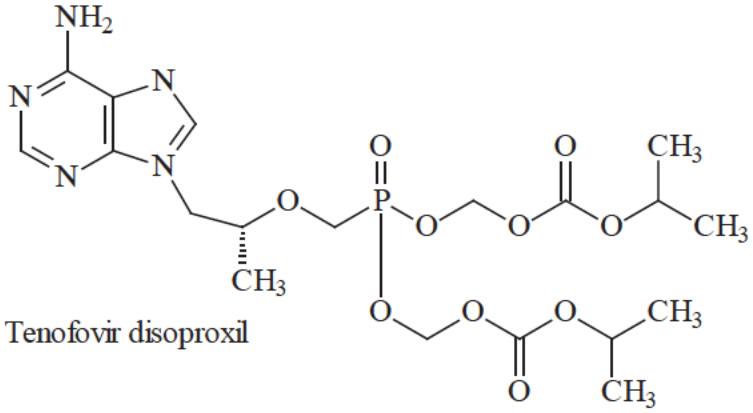
Tenofovir Alafenamide Fumarate



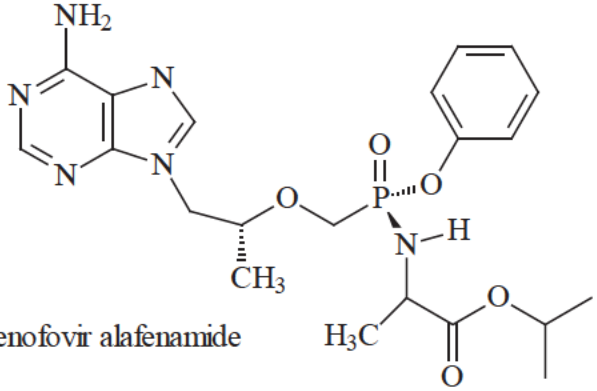
(b) (4)

. TAF is BCS Class 3 with high solubility and low permeability.

Although tenofovir disoproxil fumarate has been used for many years the new ester, tenofovir alafenamide fumarate, is a New Molecular Entity. See also the drug substance review.



Tenofovir disoproxil



Tenofovir alafenamide

P.2.1.2 Excipients

Apart from the film coats the excipients are compendial and are commonly used. (b) (4) The film coats are made from common compendial materials.

Reviewer's Assessment: Adequate

P.2.2.1 Formulation Development

The current formulation is closely related to Stribild tablets which contain elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate. (b) (4)

Formulation development took place in Phase 1. (b) (4) In Phase 1 trials it was established that the optimum dose of TAF is 10 mg (b) (4)

P.2.2.2 Overages

None

P.2.2.3 Physicochemical and Biological Properties

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: Adequate. The Phase 2, Phase 3, and commercial tablets are essentially identical. (b) (4) [redacted]

P.2.4 Container Closure System

The container closure system is a conventional HDPE bottle fitted with a child-resistant screw cap and containing a polyester coil and 3 g of silica gel desiccant. The bottle is sealed with an aluminum-faced induction seal.

Reviewer's Assessment: Adequate. The adequacy of the container-closure system will be shown by the stability data.

P.2.5 Microbiological Attributes

No microbial contamination has been found. Microbial limits testing is incorporated in the specification.

Reviewer's Assessment: Adequate. See the Quality Micro review.

2.3.P.4 Control of Excipients

P.4.1 Specifications **[Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide tablets 150/150/200/10 mg]**

The compendial excipients are as follows.

Croscarmellose sodium, NF
Hydroxypropyl cellulose, NF
Lactose monohydrate, NF
Magnesium stearate, NF
Microcrystalline cellulose, NF
(b) (4)
Sodium lauryl sulfate, NF

These excipients are tested to the current compendial standard.

(b) (4)
The applicant will continue to use these grades.

The film coating materials are the only non-compendial excipients. However they are composed of compendial ingredients as follows.

(b) (4)

(b) (4)

The FD&C Blue #2 conforms to 21 CFR 82.51 and 82.102

The following Gilead specification applies to (b) (4)

Test	Method	Acceptance criterion
(b) (4)		

The film coating materials are covered by DMF (b) (4) and Letters of Authorization to refer to this DMF, (b) (4) are provided.

P.4.2 Analytical Procedures

The analytical procedures for the compendial excipients are those contained in the USP and they do not need to be further described. The analytical methods for the film coating materials are described in reasonable detail.

P.4.3 Validation of Analytical Procedures

The analytical procedures for the compendial excipients are those contained in the USP and they do not need to be validated. The analytical methods for the film coating materials have been validated by the manufacturer.

P.4.4 Justification of Specifications

The specifications for the compendial excipients are those contained in the USP and they do not need to be further described. The specifications for the film coating materials are conventional for film coating materials.

P.4.5 Excipients of Human or Animal Origin

(b) (4)

P.4.6 Novel Excipients

None

Reviewer's Assessment:

Comments: Adequate. The film-coat is composed of compendial materials and has an acceptable specification. The other excipients are of compendial grade which is generally acceptable from a regulatory standpoint. However, some of these excipients may come in different grades. In the Amendment of 4/13/15 the applicant indicated that

(b) (4)

The applicant will continue

to use these grades.

There are no novel excipients and no excipients of human or animal origin.

2.3.P.5 Control of Drug Product

P.5.1 Specification(s)

As amended the drug product specification is as follows.

Test	Method	Acceptance criterion
Appearance	Visual	Capsule-shaped film-coated green tablets debossed with "GSI" on one side and "510" on the other Or: Capsule-shaped film-coated white tablets debossed with "GSI" on one side and "A510" on the other
Identity by retention time	HPLC*	Active peaks (b) (4) %
Identity by UV spectrum	HPLC*	Conforms to reference
(b) (4)		
Assay	HPLC TM-231	
Elvitegravir		(b) (4) %
Cobicistat		(b) (4) % (release (b) (4) %)
Emtricitabine		% (release %)
Tenofovir alafenamide		% (release %)
Degradants	HPLC TM-231 and TM-234	
(b) (4)		(b) (4) %
		% (release (b) (4) %)
		% (release %)
		%
		%
		%
		% (release (b) (4) %)
		%
		(release (b) (4))
		% (release (b) (4) %)
		% (release %)

[redacted]		[redacted] % (release [redacted] %) % (release [redacted] %) % (release [redacted] %) % (release [redacted] %) % (release [redacted] %) % (release [redacted] %) % (release [redacted] %) % (release [redacted] %)
Dose uniformity	HPLC TM-232	Conforms USP <905>
Dissolution	TM-233	
Elvitegravir		Q = [redacted] % at 60 minutes
Cobicistat		Q = [redacted] % at 20 minutes
Emtricitabine		Q = [redacted] % at 20 minutes
Tenofovir alafenamide		Q = [redacted] % at 20 minutes
Microbial limits	USP <61> and <62>	
Total aerobic		≤ 1000 cfu/g
Total yeast and mold		≤ 100 cfu/g
E. coli		Absent

*UPLC method TM-231 or HPLC method TM-232 may be used

[redacted]

Comments: Adequate. In the initial submission it was not clear how truly unknown impurities were specified. There were categories only for unknown impurities related to each active. Picking the appropriate peak to measure unidentified impurities against is not straightforward. Looking at the validation report for Method TM-231the linearity graphs on pages 82-87 relate concentration to peak area.

Active	Amount in tablet	Concentration in graph	Area count (approx)	Calculated weight of 1000 count impurity	Impurity as a percentage of the active
EVG	150 mg	[redacted]			
COBI	150 mg				
FTC	200 mg				
[redacted]					
TAF	10 mg				

A comparison is not straightforward because of the widely varying amounts of active that are present. (b) (4)

In the Amendment of 3/10/15 the applicant agrees with this reasoning and commits to adding a test for unidentified unspecified degradants, with a limit of (b) (4)%, to test method TM-231 which will be submitted in a future Amendment. This is acceptable.

P.5.2 Analytical Procedures and P.5.3 Validation of Analytical Procedures

All methods are described and have been validated. A method verification report for (b) (4) is provided.

The chromatographic and dissolution methods are discussed below.

UPLC Method TM-231 for Identity, Assay, and Degradants

(b) (4)

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(b) (4)

[redacted]

Comments: Adequate from a CMC quality control point of view. The dissolution development report is also provided. See separate Biopharm review. There is no system suitability test for resolution.

Overall Comments for Analytical Methods: Adequate. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust.

P.5.4 Batch Analyses

Batch analyses are provided for the following batches which were all manufactured by (b) (4) [redacted] The drug substance batch numbers and manufacturers are described in Table 2.

Batch	Size	Formulation
CP1105B	(b) (4) kg	White*
CP1201B	(b) (4) kg	White*
CP1203B	kg	White*
CP1204B	kg	Commercial
CP1205B	kg	Commercial
CP1208B	kg	Commercial
CP1209B	kg	Commercial
CP1303B	kg	Commercial
CP1305B	kg	Commercial
CP1307B	kg	Commercial
CP1308B	kg	Commercial
CP1310B	kg	Commercial
CP1311B	kg	Commercial
CP1313B	kg	Commercial
CP1314B	kg	Commercial
CP1315B	kg	Commercial
CP1401B	kg	Commercial
CP1402B	kg	Commercial
CP1403B	kg	Commercial
CP1306B	(b) (4) kg	Commercial with white Access film coat

(b) (4)

The following ranges of data are reported. Batches CP1105B, CP1201B, and CP1203B were tested to a slightly different specification so these results, which were acceptable, are not included.

Test	Specification		Range
	Regulatory	Release	
Appearance	Conforms		Conforms
Identity by HPLC	Conforms		Conforms
Identity by UV	Conforms		Conforms
(b) (4)			
Assay			
Elvitegravir	(b) (4) %	(b) (4) %	(b) (4) %
Cobicistat	%	%	%
Emtricitabine	%	%	%
Tenofovir alafenamide	%	%	%
Degradants			
(b) (4)			

Dose uniformity	Conforms USP <905>	(b) (4)
Elvitegravir		
Cobicistat		
Emtricitabine		
Tenofovir alafenamide		
Dissolution – range of individual values		
Elvitegravir	Q = (b) (4)% at 60 minutes	(b) (4)
Cobicistat	Q = % at 20 minutes*	%
Emtricitabine	Q = % at 20 minutes*	%
Tenofovir alafenamide	Q = % at 20 minutes*	%
Dissolution – range of mean values		
Elvitegravir	Q = (b) (4) at 60 minutes	(b) (4)
Cobicistat	Q = at 20 minutes*	
Emtricitabine	Q = at 20 minutes*	%
Tenofovir alafenamide	Q = at 20 minutes*	%
Microbial limits	USP <61> and <62>	
Total aerobic	≤ 1000 cfu/g	(b) (4) cfu/g
Total yeast and mold	≤ 100 cfu/g	fu/g
E. coli	Absent	Absent

*For batches CP1204B, CP1205B, CP1208B, CP1209B, and CP1303B there are no 20 minute dissolution vales. 15 Minute values are used instead.

For most batches earlier versions of the analytical methods were used. These methods are listed in Table 26, see P.8 for a discussion.

Comments: Adequate. All 20 batches meet the specification.

P.5.5 Characterization of Impurities

(b) (4)

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(b) (4)

Reviewer's Assessment: Adequate.

R.2 Comparability Protocols

14. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Applicant's Information: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

There are no comparability protocols.

Environmental Assessment Or Claim Of Categorical Exclusion

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 elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in the aquatic environment is expected to be less than 1 part per billion. The applicant certifies that to the best of their knowledge no special circumstances exist.

Comments: Adequate. The claim is reasonable and should be accepted.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

This NDA is recommended for approval from the CMC drug product perspective. All CMC issues concerning the drug product have been satisfactorily resolved. The composition, manufacturing process, and specifications for the tablets are appropriate and the expiration dating period of 24 months is supported by adequate data. The container-closure systems and labeling are appropriate.

George Lunn July 6, 2015

Supervisor Comments and Concurrence:
I concur July 8, 2015

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

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Batch Formula

15. Does the provided batch formula reflect the proposed composition and that of the registration batches?

Applicant's Information:

The proposed commercial batch size for elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide (E/C/F/TAF) tablets is (b) (4) kg (corresponding to approximately (b) (4) tablets), based on the film-coated tablet batch weight. The manufacturing formula for the commercial batch size is given below:

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature: Adequate

As amended, the applicant made the following commitments (b) (4) [redacted]

(b) (4)

In conclusion, the applicant provided sufficient data (16 clinical and stability batches) to demonstrate the consistency of the proposed commercial manufacturing process at the proposed commercial scale.

Lin Qi 6/18/2015

Supervisor Comments and Concurrence:

Applicant's response to the IR comments related to the manufacturing process is acceptable.

U. Atwal / 06/18/2015

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

The following sites are responsible for the manufacture, release testing, packaging and labeling and stability testing of the four drug substances Cobicistat (COBI), Elvitegravir (EVG), Emtricitabine (FTC) and Tenofovir Alafenamide Fumarate (TAF) which is a new molecular entity (NME):

Facility Name	FEI	Responsibility	Initial Risk Assessment	Current Status	Final Recommendation
(b) (4)			Low	(b) (4)	Acceptable
			Low		Acceptable based on EIR review of (b) (4) PAI inspection and district recommendation

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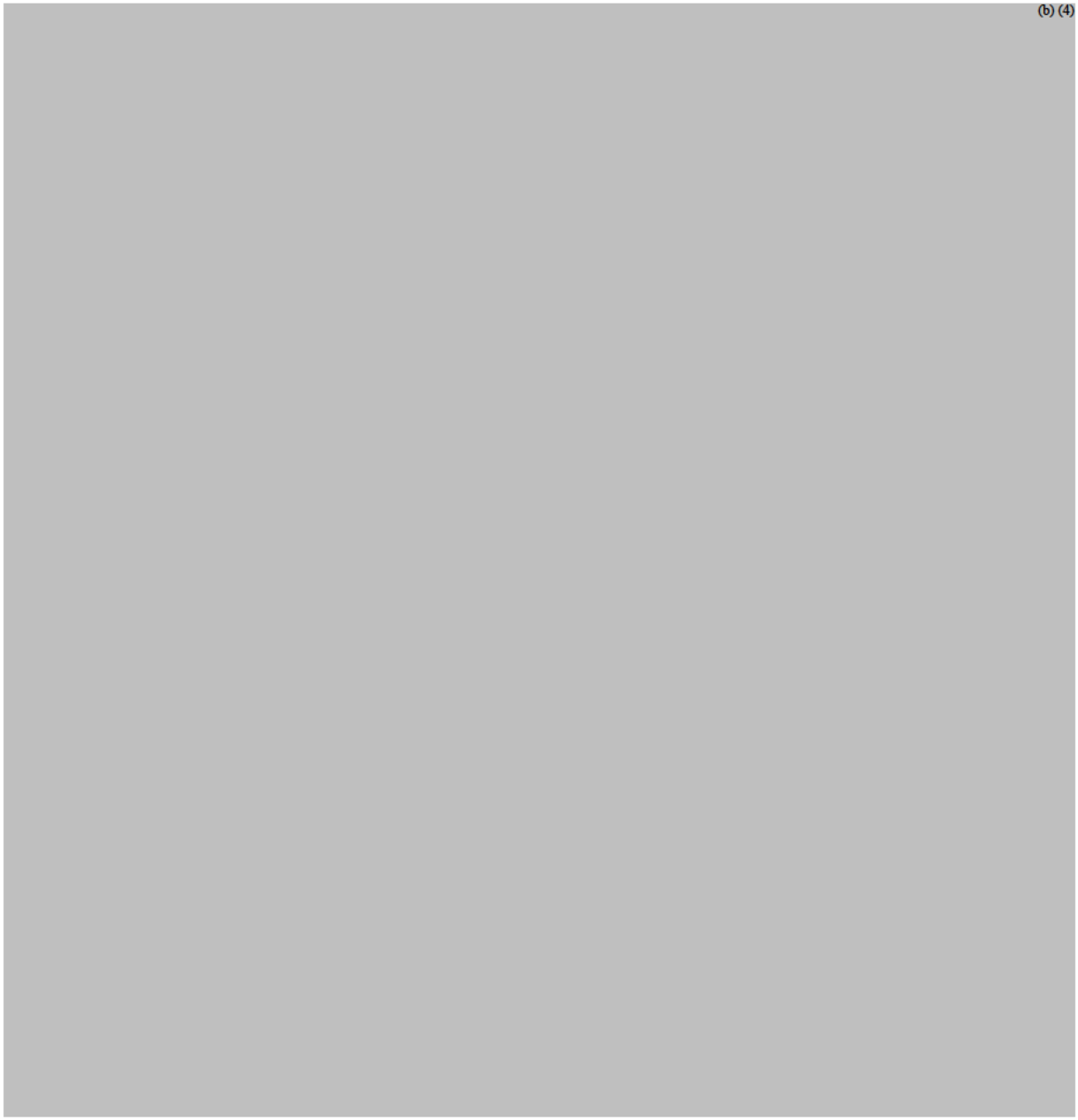
(b) (4)



OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Krishna Ghosh , 7/8/2015 - Recommend for approval

The facilities listed in this submission have been carefully reviewed. Initial risk assessment were conducted and GMP inspections were issued based on the (2, 3, 4 years rule for GMP inspection) in Nov 2014 prior to the CDER policy change with regards to surveillance inspection. In depth review was conducted for each of the facilities according to the previous inspection history, nature of FDA 483 and firm's response, product recalls, product characteristics, as well as the FDA observations related to the current manufacturing process of the drug substance or the drug product. (b) (4) was submitted as a manufacturer of Emitricitabine, however on Feb 6, 2015 an amendment to NDA 207561 was submitted to remove this facility from the application. The Feb 6th 356h reflects the updated status. Two of the facilities were identified to have moderate risk during initial risk assessment but rest of the firms had low risk. Based on the review of the Establishment Inspectional reports along with district recommendations for the GMP inspections, it is recommended that all the facilities in this submission are acceptable until 11/16/2015.

Supervisor Comments and Concurrence:

I concur.
Grace McNally, Acting Branch Chief, Division of Inspectional Assessment, OPF, OPQ
7/8/2015

ASSESSMENT OF BIOPHARMACUETICS INFORMATION

The Biopharmaceutics assessment is focused on the evaluation of the dissolution information supporting the proposed dissolution method and acceptance criteria.

DISSOLUTION METHOD

One dissolution method is being proposed as a quality control tool for the four APIs of the E/C/F/TAF tablets as presented in Table 1.

Table 1. Proposed Dissolution Method

Apparatus	Rotation	Volume	Temp	Medium	Acceptance
USP II	100 rpm	1000 mL	37 °C	50 mM citrate buffer 2.0% w/v Polysorbate 80 pH 5.5	EVG: Q = (b)(4)% at 60 min COBI, FTC, and TAF: Q= (b)(4)% at 20 min

Dissolution Medium Selection

(b) (4)

[redacted]

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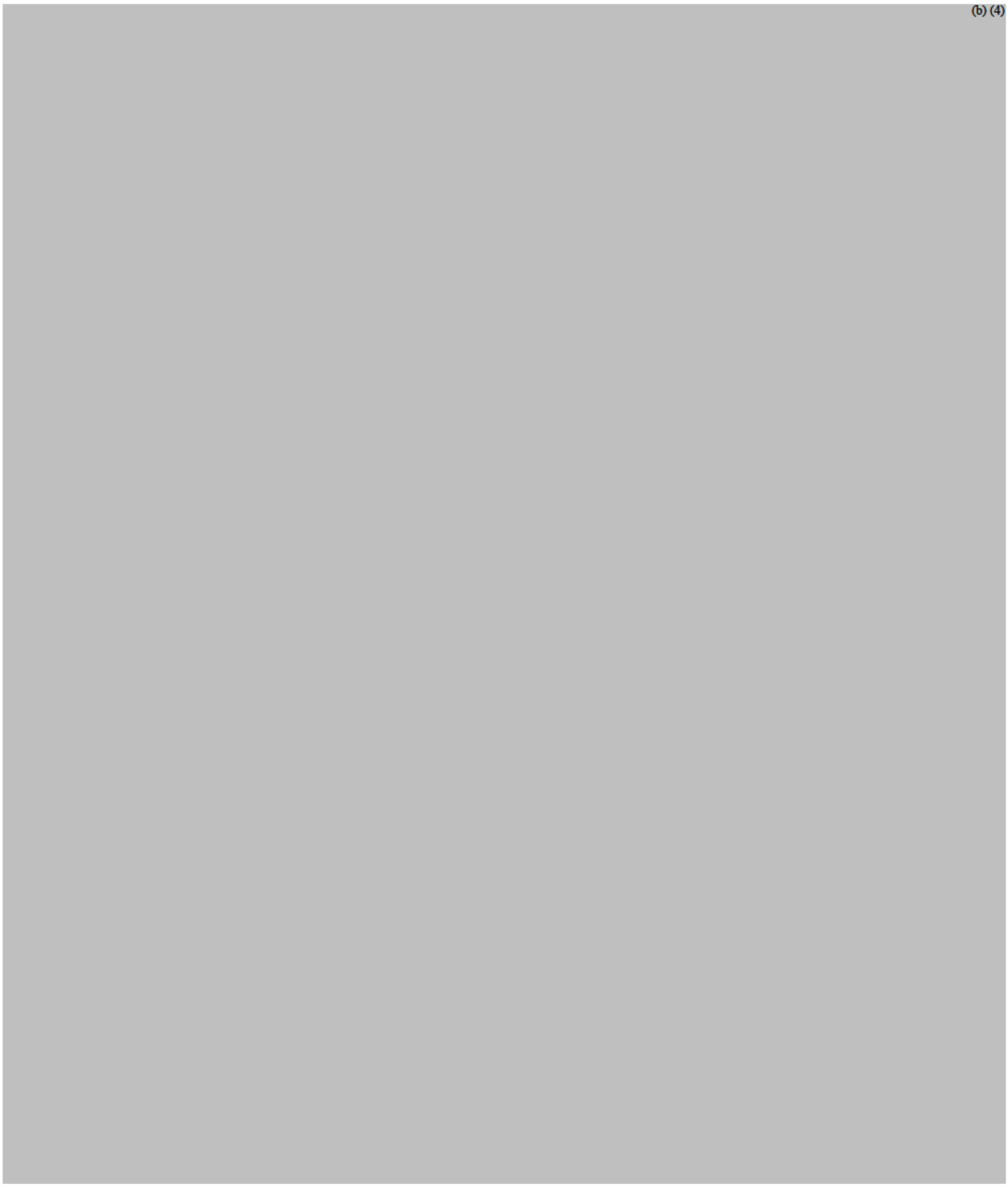
(b) (4)



DISSOLUTION METHOD ACCEPTANCE CRITERIA

The Applicant proposes the following acceptance criteria: Q = (b) (4)% at 20 minutes for FTC, TAF, and COBI and Q = (b) (4)% at 60 minutes for EVG. The Applicant provided data – initial through 18 months of stability at normal conditions – for the following batches: CP1204B, CP1209B, CP1303B, CP1306B, CP1307B, CP1308B, and CP1401B (see

3.2.P.8 for stability detailed stability data). The provided dissolution data supported Q = (b)(4)% at 15 minutes for FTC, TAF, and COBI and Q = (b)(4)% at 45 minutes for EVG. The recommended acceptance criteria were conveyed to the Applicant in an IR (submitted to the Applicant on 25-JUN-2015). The Applicant responded to the IR on 02-JUL-2015. The Applicant provided a justification for maintaining the proposed acceptance criteria (Q = (b)(4)% at 20 minutes for COBI, FTC, and TAF and Q = (b)(4)% at 60 minutes for EVG) instead of the recommended criteria (Q = (b)(4)% at 15 minutes for COBI, FTC, and TAF and Q = (b)(4)% at 45 minutes for EVG). (b)(4)

(b)(4)

he Applicant provided stability data at 12 months for Batch CP1204B1, which is representative of the formulation used in the Phase 3 clinical trial, to support the proposed criteria (Table 2). No trends in dissolution during the stability studies were observed.

Table 2. EVG Dissolution Data for E/C/F/TAF Tablets Lot CP1204B1 at 12-Month Time Point at the Storage Condition of 25 °C/60% RH

Dissolution Time Point (minutes)	Percent Dissolved							
			Individual Results					
	Mean	SD	1	2	3	4	5	6
30	(b)(4)							
45								
60								

Reviewer's Assessment: Dissolution Method Acceptance Criteria

The justification provided by the Applicant to maintain the proposed acceptance criteria is ACCEPTABLE. The proposed sampling time point (20 minutes) discriminates batches manufactured with "out of range" conditions. The proposed time point is also not likely have an effect on the clinical performance of the product (b)(4) *In the case of EVG, the Applicant provided 102 combined data points and demonstrated that the variability at 45 minutes may lead to rejection of batches that have been shown to be clinically acceptable.*

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

The dissolution test and acceptance criteria, based on the information summarized above, are adequate.

18. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

There was no bridging necessary for the proposed drug product. The formulation used in the Phase III pivotal efficacy trial and the To-be-marketed formulation was developed early in Phase I and was used for the clinical development of the drug product.

Reviewer's Assessment:

There was no bridging necessary for the proposed drug product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature: RECOMMENDED FOR APPROVAL

The Applicant has provided sufficient data to support the selection of the dissolution method parameters and to demonstrate the discriminating ability of the proposed method. The stability data (initial time point through 18 months) support the proposed dissolution method acceptance criteria. As such, NDA 207561 is RECOMMENDED FOR APPROVAL from a Biopharmaceutics perspective.

Apparatus	Speed	Vol	Temp	Medium	Acceptance
USP II	100 rpm	1000 mL	37 °C	50 mM citrate buffer 2.0% w/v Polysorbate 80 pH 5.5	**EVG** Q = (b)(4)% at 60 min **COBI/FTC/TAF** Q= (b)(4)% at 20 min

08-JUL-2015

Salaheldin S. Hamed, Ph.D
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:
I concur with Dr. Hamed's recommendation and conclusions.
08-JUL-2015

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

ASSESSMENT OF MICROBIOLOGY

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

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) with NMT 10^3 total aerobic microbial count, 10^2 total yeast and molds, and the absence of *Escherichia coli*.

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability protocol.

Reviewer's Assessment:

The Microbial Limits specification for Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) tablet is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

2.3.P.6 Reference Standards or Materials

20. 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?

Not applicable for this solid oral dosage form.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

21. 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)?

    Not applicable.

22. 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?

    Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
This application is recommended for approval by product quality microbiology.
December 2, 2014

Jessica Cole, PhD
OPF/DMA/Branch III

Supervisor Comments and Concurrence:
I concur.
December 2, 2014

Bryan Riley, PhD
OPF/DMA/Acting Branch Chief Branch II

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]™ (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) tablets, for oral use. Initial U.S. Approval: 2015

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Established Name:	Adequate
Dosage form, route of administration	Dosage: Route:	Adequate
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Adequate

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 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg tenofovir alafenamide fumarate).
The tablets are green, capsule-shaped, film-coated tablets, debossed with "GSI" on one side of the tablet and the number "510" on the other side of the tablet.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Adequate
Strengths: in metric system		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

Conclusion: **Adequate**

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

[TRADENAME] is a fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide for oral administration.

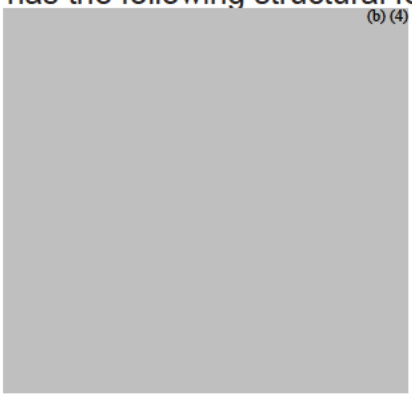
- Elvitegravir is an HIV-1 integrase strand transfer inhibitor. (b) (4)
- Cobicistat is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. (b) (4)
- Emtricitabine is a synthetic nucleoside analog of cytidine. (b) (4)
- Tenofovir alafenamide is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg tenofovir alafenamide fumarate). The tablets include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium lauryl sulfate . The tablets are film-coated with a coating material containing indigo carmine aluminum lake, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Elvitegravir: The chemical name of elvitegravir is 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

It has a molecular formula of $C_{23}H_{23}ClFNO_5$ and a molecular weight of 447.9. It has the following structural formula:

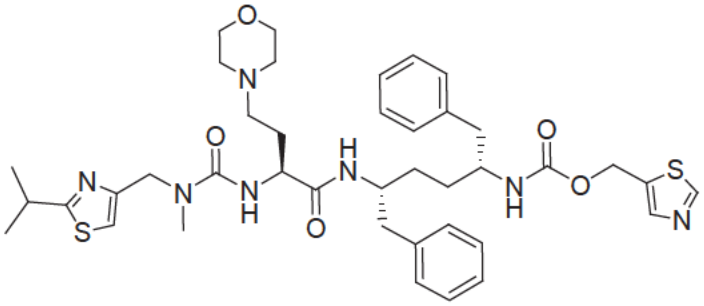
(b) (4)



Elvitegravir is a white to pale yellow powder with a solubility of less than 0.3 micrograms per mL in water at 20 °C.

Cobicistat: The chemical name for cobicistat is 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl), 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*).

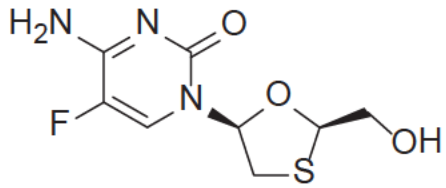
It has a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0. It has the following structural formula:



Cobicistat is adsorbed onto silicon dioxide. Cobicistat on silicon dioxide drug substance is a white to pale yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

Emtricitabine: The chemical name of emtricitabine is 4-Amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. Emtricitabine 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.

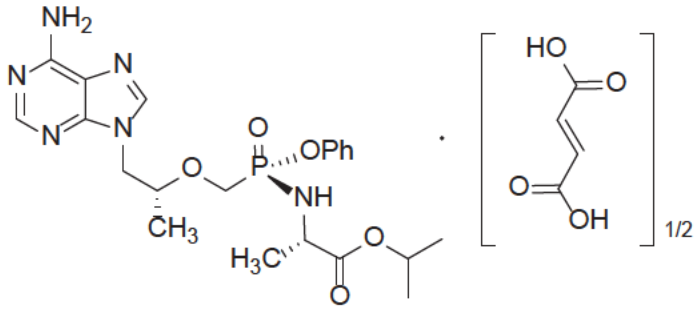
It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.25. It has the following structural formula:



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

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).

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



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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Adequate
Dosage form and route of administration		Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Adequate
Statement of being sterile (if applicable)	Not applicable, this is a non-sterile tablet.	N/A
Pharmacological/ therapeutic class		Adequate
Chemical name, structural formula, molecular weight		Adequate
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		Adequate

Conclusion: Adequate

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

16 HOW SUPPLIED/STORAGE AND HANDLING

[TRADENAME] tablets are green, capsule-shaped, film-coated tablets, debossed with "GSI" on one side of the tablet and the number "510" 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.
- Do not use if seal over bottle opening is broken or missing.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		Adequate
Storage conditions		Adequate

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)		Adequate

Conclusion: Adequate

2. Labels

1) Immediate Container Label

US Container Label

Access Container Label

(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))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		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)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
Others	Equivalency statement was added (July 7)	

*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.
**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) Cartons

There is no US carton. The Access carton design is as follows.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		N/A
Sterility Information (if applicable)		N/A
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage Conditions		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)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)		Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		N/A

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

All Product Quality labeling issues have been resolved, and support approval.

George Lunn July 8, 2015

Supervisor Comments and Concurrence:
I concur July 8, 2015

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

II. List of Deficiencies To Be Communicated

All deficiencies have received adequate responses. There are no remaining deficiencies or information requests that need to be conveyed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: George Lunn, CMC Reviewer
Jeff Medwid, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: george.lunn@fda.hhs.gov/Jeffrey.Medwid@fda.hhs.gov
Phone: (301) 7961701/(301)-7962204
Fax. (301)-7969877
Through: Stephen Miller, CMC Lead
Phone: (301)-7961418
And Youbang Liu
ONDQA Methods Validation Project Manager
Phone: (301)-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 207561

Name of Product: Elvitegravir/cobicistat/emtricitabine/Tenofovir alafenamide, fixed dose combination tablets

Applicant: Gilead Sciences, Inc.

Applicant's Contact Person: Erik Berglund or Mae J. Lai

Address: 333 Lakeside Dr, Foster City, California, 94404

Telephone: (650)-5243984 OR (650)-5243853 Fax: (650)-5225489

Date NDA Received by CDER: 11/05/2014	Submission Classification/Chemical Class: NME
Date of Amendment(s) containing the MVP:	Special Handling Required: No
DATE of Request: **12/15/2014**	DEA Class: N/A
Requested Completion Date:9/5/2015	**Format of Methods Validation Package (MVP)**
PDUFA User Fee Goal Date: **11/5/2015**	☐ Paper X Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as descr bed in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference # EDR 3.2R	**METHODS VALIDATION REQUEST**	NDA # 207561

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	
Specifications/Methods for New Drug Substance(s)	
Specifications/Methods for Finished Dosage Form(s)	
Supporting Data for Accuracy, Specificity, etc.	
Applicant's Test Results on NDS and Dosage Forms	
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
TM231	For identity, assay and degradant by UPLC Method		**0**	
TM232	For Identity and content Uniformity by HPLC Method		**0**	
T234	For Specific Emtricitabine,Tenofovir Alafenamide degradant by UPLC Method		**0**	
TM233	Dissolution Method		**0**	
TM230	Elemental Impurity Analysis of Tenofovir Alafenamide Fumarate (GS-7340-03) by ICPMS		**0**	
TM-229	Determination of Identity and (b) (4) Content in Tenofovir Alafenamide Fumarate Drug Substance by HPLC		**0**	
STM-0049.01	Verification of STM-0049.01: Clarity of Solution Determination of Tenofovir Alafenamide (TAF) Fumarate Drug Substance		**0**	

TM-228	Validation of (STM-2055): Residual Solvent and [redacted] (b) (4) Content of Tenofovir Alafenamide Fumarate Drug Substance by Headspace Gas Chromatography		**0**	
TM-236	Validation of (STM-3155): [redacted] (b) (4) Content in Tenofovir Alafenamide Fumarate by HPLC-MS"		**0**	
TM-227	Validation of (STM-2013): Identification, Assay, and Impurities of Tenofovir Alafenamide Fumarate Drug Substance by HPLC		**0**	

Additional Comments:

EDR Location: \\CDSESUB1\evsprod\NDA207561\207561.enx
EDR Location: \\CDSESUB1\evsprod\NDA207561\0000

Some Relevant Documents informations: ABVAL-R0695.01, ABVAL-R0706.01, ABVAL-R0727.00, ABVAL-R0751.02, ABVAL-R0871.01, QAVAL-1850R.01

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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

/s/

AKHTAR R SIDDIQUI
12/15/2014

GEORGE LUNN
12/15/2014

JEFFREY B MEDWID
12/16/2014

YOUBANG LIU
12/18/2014