

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208215Orig1s000

CHEMISTRY REVIEW(S)

Approval

NDA 208215

Review #2

Drug Name/Dosage Form	Emtricitabine and Tenofovir Alafenamide
Strength	200mg/25mg (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Orig	04/07/15	Product Quality
Amendment	06/12/15	Product Quality
Amendment	07/14/15	Product Quality
Amendment	08/06/15	Product Quality
Amendment	09/04/15	Product Quality
Amendment	12/08/15	Product Quality
Amendment	01/08/16	Product Quality
Amendment	01/11/16	Product Quality (Container Labels)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker, PhD	OPQ/ONDP/NDAPI/Branch I
Drug Product	Shrikant (Suresh) Pagay, PhD	OPQ/ONDP/NDPI/Branch III
Process	Ying Wang, PhD	OPQ/OPF/DIV-1/BRANCH-III
Microbiology	Ying Wang, PhD	OPQ/OPF/DIV-1/BRANCH-III
Facility	Frank Wackes	OPQ/OPF/DIA/Branch II
Biopharmaceutics	Gerlie Gieser, PhD	OPQ/ONDP/DB/Branch I
Regulatory Business Process Manager	Maryam Changi, PharmD	OPRO/Div I/ Branch-I
Application Technical Lead	Stephen Miller, PhD	OPQ/ONDP/NDPI/Branch III
ORA Lead	Paul Perdue, PhD	ORA/OMPTO/MIN-DO

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED (b) (4)	STATUS	DATE REVIEW COMPLETED	COMMENTS ***
				Adequate	11/9/2012	
				Adequate	5/29/2014	
				Adequate	4/24/2012	
				Adequate	10/25/2012	
				Adequate	9/10/2012	
				Reviewed Madurawe	12/7/2004	
				Adequate	1/27/2014	
				--	--	
				Adequate	10/24/2012	
				--	--	
				Adequate	10/4/2013	
				Adequate	8/14/2014	
				Reviewed Puttagunta	6/7/2005	
				Adequate	8/19/2014	
				Adequate	3/21/2012	
				Adequate	9/18/2014	
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Type III and Type IV DMFs: Adequate information is provided in the NDA and reviewed under appropriate sections.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	111851	IND for this product
NDA	208351	Related product (emtricitabine, rilpivirine and TAF) currently also under NDA review
NDA	207561	Only approved NDA for a product containing TAF (in a 4-drug combination tablet)

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Environmental Assessment	NA	James Laurenson provided advice regarding the Categorical Exclusion statements for several TAF-containing NDAs.		

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the quality of the drug substances and this drug product. The assessment of the manufacturing facilities is complete and the application was recommended for approval.

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

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

We also acknowledge receipt of information related to DESCOPY[®] (emtricitabine and tenofovir alafenamide), 200/25 mg (b) (4) fixed-dose combination tablet for your Gilead Access Program that was reviewed as part of this application.

3. Benefit/Risk Considerations

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

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

II. Summary of Quality Assessments

A. Drug Substance [Tenofovir Alafenamide Fumarate] Quality Summary

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

(b) (4) Note that a lower dose of TAF fumarate (10mg/day) is used for treatment regimens that include a PK booster (such as the Genvoya tablet, (b) (4)

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

A. Drug Substance [Emtricitabine] Quality Summary

See NDA 21752 and detailed review notes, below.

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

- a. Strength: 200mg/25mg (b) (4)

- b. Description/Commercial Image of US Product:
200/25 mg tablets are blue, rectangular-shaped, film-coated tablets with “GST” debossed on one side and “225” on the other side.

(b) (4)

Description/Commercial Image of Access Product:

Identical except that the film coats are white, and the second sides are debossed “A25” (b) (4) for the 200/25mg and (b) (4).

- c. Summary of Product Design: The product is a monolithic tablet with two drug substances, and is produced using conventional pharmaceutical processes. The specification includes tests for appearance, identity, water, assay, degradants, uniformity, dissolution, and microbial limits. The specification is largely conventional for an immediate release solid oral dosage form and a satisfactory justification is provided. The limit for (b) (4) was reduced from NMT (b) (4)% to NMT (b) (4)% to reduce the risk of TAF-associated degradants exceeding their acceptance criteria on storage. The degradants are toxicologically qualified at the proposed limits. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust. Satisfactory batch analyses are provided for 5 batches of each strength. Four of these batches are (b) (4). Also, satisfactory batch analyses are provided for 3 batches of (b) (4) of the Access tablet; the batch size of Access tablets is (b) (4) per batch.
- d. List of Excipients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and indigo carmine aluminum lake (200/25mg) (b) (4). The magnesium stearate is from (b) (4).
- e. Process Selection (Unit Operations Summary):

(b) (4)

- f. Container Closure: The tablets are packaged in HDPE bottles containing 30 tablets, a silica gel desiccant, polyester coil, and closed with a child-resistant closure.
- g. Expiration Date & Storage Condition: The applicant claims a 24 month expiration dating period with the storage statement: “Store below 30°C”.

This is supported with a statistical analysis of the available stability data, including the 30°C/75% RH long-term data, and is acceptable.

- h. Twelve months of satisfactory stability data are provided for three batches stored at 25°C/60% RH and 30°C/75% RH as well as 6 months stored at 40°C/75% RH. There are no out of specification results. The only obvious trends are an increase in TAF impurities (b) (4) and total TAF impurities with time and temperature. The stability behavior of the US and Access tablets are the same .
- i. List of Co-Packaged Components: None

C. Summary of Drug Product Intended Use

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

D. Biopharmaceutics Considerations

a) BCS Designation:

- Drug Substance: No official designation has been requested in this application, (b) (4)
- Drug Product: (b) (4)

b) Biowaivers/Biostudies

- Biowaiver Requests:—N/A
- PK studies(pivotal BA/BE Studies): GS-US-311-1472 and GS-US-311-1473
- IVIVC: N/A

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

a) (suggested text edits for OCP reviewer consideration) **Section 12.3**

Pharmacokinetics:

In single-dose crossover studies involving healthy subjects who received test and reference treatments with a moderate-fat, moderate calorie breakfast, the plasma AUC and Cmax of emtricitabine (FTC) and tenofovir alafenamide (TAF) were comparable between DESCOVY® (F/TAF) 200/25 mg fixed dose combination tablet and GENVOYA® EVG/COBI/FTC/TAF (150/150/200/10 mg) fixed-dose combination tablet, and between DESCOVY® 200/10 mg (coadministered with EVG 150 mg and COBI 150 mg) and GENVOYA®.

(b) (4)

Additional labeling recommendations

- a. Within the parts of Section 11 where the tablet composition and nature of the drug substances are described we recommend that full names be used rather than the acronyms, FTC and TAF.
- b. We note that the list of active ingredients in the Patient Information section includes (b) (4) which was not the case for the Genvoya tablet. From the Prod Qual perspective, it seems preferable to omit (b) (4) except when describing the drug substance (as in one part of Section 11).
- c. At an appropriate time, please submit container/carton labels for both the US and Access products with "Tradename" replaced as appropriate.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: 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
0.9.2342.19200300.100.1.1=1300087013
Date: 2016.02.23 20:09:02 -05'00'

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

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This Biopharmaceutics assessment is focused on the evaluation of the following:

1. the proposed dissolution method,
2. the proposed dissolution acceptance criteria, and
3. the three BA/BE studies.

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

Yes.

The in vitro dissolution test is part of the QC specifications for the proposed product's release and stability testing. The proposed dissolution test and the revised acceptance criterion ($Q^{(b)(4)}$ % at 30 minutes) are adequate.

Dissolution method:

The proposed dissolution method for emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) fixed dose combination (FDC) product is summarized below.

USP Apparatus II (paddle), operated at 75 rpm
Dissolution medium: 500 mL 50 mM sodium citrate buffer,
pH 5.5, 37 °C

Given that both FTC and TAF are highly soluble, the dissolution medium volume selected was 500 mL (lower limit of the range recommended for Apparatus II). Compared to $^{(b)(4)}$ rpm, a paddle speed of 75 rpm ensured complete dissolution within 30 minutes, and lower variability. The dissolution of FTC and TAF was equivalent in the medium with and without deaeration.

The Applicant claims that the proposed dissolution method is appropriate as a quality control test because $^{(b)(4)}$

$^{(b)(4)}$

$^{(b)(4)}$

$^{(b)(4)}$

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immediately following this page

Reviewer's Assessment:***Dissolution Method***

The reviewer agrees with the Applicant that the dissolution method proposed for QC release and stability testing of the two strengths of the FTC/TAF FDC tablet is discriminating, while maintaining TAF stability in solution.

The proposed dissolution method is a suitable quality assurance test of batch-to-batch consistency as it was shown to be able to detect intentionally manufactured aberrant FTC/TAF FDC tablets. There was an apparent trend of slightly decreased dissolution rate of FTC and TAF from the proposed commercial (US Presentation) tablets over 12 months of long-term storage suggesting that the proposed dissolution test is a suitable quality assurance test, in addition to stability-indicating assays.

Dissolution acceptance criterion:

The Applicant's proposed dissolution acceptance criteria are:

- [REDACTED] (b) (4)
- FTC/TAF 200/25 mg tablets: Q = 75% for the amount of FTC and TAF dissolved at 30 minutes

Per ICH Q6A Decision Tree 7, a single point acceptance criterion with a lower limit is acceptable. The proposed dissolution acceptance criteria are based on the dissolution results (Figure 38-1) from clinical and development batches of FTC/TAF tablets. (b) (4)

[REDACTED]

Reviewer's Assessment:***Dissolution Acceptance Criteria***

In general, the dissolution acceptance criteria should be based on the time point where at least (b) (4) % (Q) dissolution is achieved. Note that Lots CR1308B and [REDACTED] (b) (4) 200/25 mg tablets, respectively) were shown to be bioequivalent to reference treatment in all three BA/BE Studies conducted by the sponsor. At the time of lot release, these (b) (4) lots showed (b) (4) % dissolution in (b) (4) minutes (Table 38-1).

Table 38-1. Summary of In Vitro Dissolution Profiles of FTC and TAF from Descovy® [REDACTED] (b) (4) and FTC/TAF 200/25 mg Tablets (CR1305B) used in Pivotal Bioequivalence Studies (b) (4) GS-1473 (b) (4)

[REDACTED]

(b) (4)

(b) (4)

This recommendation was communicated in an information request dated 8/30/2015. The Applicant responded on 9/4/2015, and agreed to the FDA recommendation to use $Q = \frac{(b)(4)}{(4)} 0\%$ within 30 minutes as the dissolution acceptance criterion for the 200/25 mg strength tablet. As requested by the FDA, revised Drug Product specification tables were included in the Applicant's response.

Relative Bioavailability Studies:

To evaluate relative bioavailability, three single-dose, crossover studies involving healthy subjects who received test and reference treatments with a moderate-fat, moderate-calorie breakfast were conducted.

Comparable bioavailability of FTC/TAF FDC tablet strengths 200/25 mg (unboosted) (b) (4) to reference treatment (either E/C/FTC/TAF 150/150/200/10 mg FDC tablet or FTC 200mg capsule + TAF 25 mg tablet) was established in clinical studies (Table 38-2 to Table 38-4). FTC and TAF are highly soluble compounds (i.e., BCS-1 and BCS-3, respectively). In vitro-in vivo correlation (IVIVC) for FTC and TAF is not expected for this *immediate-release* FDC tablet.

Table 38-2. Study GS-US-311-1473: Sponsor's Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Set)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC _{last} (ng•h/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32 (96.48, 104.31)
AUC _{inf} (ng•h/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54 (94.61, 102.62)
C _{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63 (95.46, 112.49)
FTC PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC _{last} (ng•h/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01 (88.88, 91.16)
AUC _{inf} (ng•h/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20 (89.06, 91.35)
C _{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26 (94.57, 100.03)

Source: m5.3.1.2, GS-US-311-1473, Section 15.1, Tables 4.2.1, 4.2.2, 5.1, 5.3.1, and 5.3.2

Adapted from NDA 208-215, Clinical Summary 2.7.1, Table 15
F = FTC; TAF (as free base)

(b) (4)

Table 38-4. Study GS-US-311-1088: Sponsor's Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Set)

	Mean (%CV) by Treatment		GLSM Ratio (90% CI), %
	F/TAF (Test) (N = 55)	FTC+TAF (Reference) (N = 55)	
TAF PK Parameter			
AUC _{last} (ng•h/mL)	265.1 (42.9)	253.6 (33.7)	102.68 (95.78, 110.09)
AUC _{inf} (ng•h/mL)	273.8 (45.4) ^a	257.9 (34.4) ^b	105.77 (97.26, 115.01)
C _{max} (ng/mL)	232.4 (51.9)	248.1 (44.7)	92.59 (82.31, 104.16)
FTC PK Parameter			
AUC _{last} (ng•h/mL)	9175.8 (17.4)	9596.0 (22.9)	96.16 (94.29, 98.08)
AUC _{inf} (ng•h/mL)	9387.7 (17.3)	9821.6 (22.5)	96.09 (94.24, 97.96)
C _{max} (ng/mL)	1873.5 (27.2)	1767.6 (22.8)	104.98 (100.75, 109.39)

^a n = 43^b n = 48

Source: m5.3.1.2, GS-US-311-1088, Section 15.1, Tables 5.1, 5.2, and 6.1

Adapted from NDA 208-215, Clinical Summary 2.7.1, Table 16

F = FTC; ; TAF (as free base)

Reviewer's Assessment:***Relative Bioavailability of DESCOVY® (FTC/TAF) FDC tablets versus GENVOYA® (E/C/FTC/TAF) FDC tablet***

Based on the reviewer's confirmatory analyses, the plasma AUC and C_{max} of both FTC and TAF (as free base) achieved with the lot of DESCOVY (b) (4) the lot of DESCOVY 200/25 mg (unboosted) FDC tablet tested in pivotal (b) (4) GS-US-311-1473, respectively, were within pre-specified bioequivalence acceptance limits, as compared to one of the lots of GENVOYA® (EVG/COBI/FTC/TAF 150/150/200/10 mg) FDC tablet evaluated in clinical efficacy trials (see Table 38-5). Additionally, in Study GS-US-311-1088, the lot of the DESCOVY 200/25 mg tablet (the same as that tested in Study 1473) had FTC and TAF bioavailability comparable to that of combination treatment with EMTRIVA (FTC) 200 mg capsule and TAF 25 mg tablet.

(b) (4)

GS-US-311-1473 (n=83 ^c)	Test: FTC/TAF (200/25 mg) FDC tablet [Lot CR1305B2]; unboosted Reference: E/C/FTC/TAF (150/150/200/10 mg) FDC tablet [Lot CPI310B1]	FTC	90.18 (88.87-91.51)	90.03 (88.73-91.35)	96.14 (93.51-98.83)
		TAF	98.13 (94.17-102.25)	98.19 (94.19-102.35)	98.32 (90.17-107.21)
GS-US-311-1088 (n=38 ^c)	Test: FTC/TAF (200/25 mg) FDC tablet [Lot CR1305B2]; unboosted Reference: FTC 200 mg capsule + TAF 25 mg tablet	FTC	93.76 (91.69-95.88)	94.08 (91.92-96.30)	104.82 (99.97-109.90)
		TAF	107.07 (98.02-116.95)	107.18 (98.12-117.09)	95.72 (82.53-111.01)

^a "Bioequivalence" of FTC and TAF in the FTC/TAF FDC to the FTC and TAF components in E/C/FTC/TAF FDC was concluded if the 90% CI of the GLSM ratio of the PK parameters for each analyte between 2 formulations fell within the prespecified bioequivalence boundary of (b) (4) to (b) (4).

^b F or FTC (emtricitabine); TAF (tenofovir alafenamide; TAF (as free base)); COBI or C (cobicistat); EVG or E (elvitegravir); FDC (fixed dose combination)

^c Reviewer's confirmatory analyses: using Phoenix 6.4 software; includes only the subset of subjects with a complete set of emtricitabine (FTC) and TAF plasma AUCinf, AUClast, Cmax and Tmax

^d For completeness, table includes the "BE" analysis for the COBI and EVG analytes.

Therefore, this Reviewer concludes that (b) (4)
(b) (4) the proposed FTC/TAF 200/25 mg FDC tablet have comparable bioavailability to the reference E/C/FTC/TAF 150/150/200/10 mg FDC tablet which was evaluated in clinical efficacy trials.

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

(b) (4)

Reviewer's Assessment:

The reviewer concurs with the Applicant's assessment that a bridging study between clinical research formulations and the proposed US commercial product is not needed, since the US Presentation tablet formulations tested in the pivotal BA/BE studies are identical to the ones intended for commercialization.

As shown in Figure 38-1 above, the dissolution rates of FTC and TAF (b) (4)

(b) (4)

In response to a FDA information request, the Applicant provided the dissolution profiles for additional lots of Access tablets, and provided clarification regarding the

(b) (4)

(b) (4)

Figure 39-1. Dissolution of FTC and TAF from US Presentation Tablets and Access Tablets

(b) (4)

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS****Reviewer's Conclusion, Recommendation and Signature:**

- The Applicant's proposed dissolution method for Descovy® (FTC/TAF) 200/25 mg (b) (4) FDC tablets (test conditions shown below) is acceptable.
USP Apparatus II (paddle), operated at 75 rpm
Dissolution medium: 500 mL 50 mM sodium citrate buffer, pH 5.5, 37 °C
- The revised dissolution acceptance criterion of $Q = \frac{(b) (4)}{(4)}\%$ at 30 minutes for (b) (4) Descovy® tablets is acceptable.
- Based on the reviewer's confirmatory analyses of pivotal BA/BE data, when given as single doses to healthy subjects with a moderate-fat, moderate calorie breakfast, unboosted Descovy® FTC/TAF 200/25 mg FDC tablet [Lot CR1305], (b) (4) are bioequivalent to GENVOYA® (EVG/COBI/FTC/TAF 150/150/200/10 mg) FDC tablet [Lot CP1310B1] previously evaluated in clinical efficacy trials. Alternate trade dress or Access tablets (b) (4) 200/25 mg that were manufactured at (b) (4)

From the Biopharmaceutics perspective, NDA 208-215 for FTC/TAF FDC tablets (b) (4) 200/25 mg is recommended for APPROVAL.

11/5/2015

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer,
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I concur with Dr. Gieser's recommendation and conclusions.

11/5/2015

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

ASSESSMENT OF MICROBIOLOGY

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

Per Applicant, F/TAF tablets are an excellent candidate for reduced microbial testing for product release and stability evaluation (USP <1112>) because F/TAF tablets (b) (4)

Furthermore, F/TAF tablets showed no significant bioburden and absence of indicator organisms at release and after storage at 25 °C/60% RH and 30 °C/75% RH for 12 months, and at 40 °C/75% RH for 6 months. Based on these data, microbiological examination on F/TAF tablets is deemed unnecessary according to ICH Q6A, Decision Tree 8. However, in order to assure drug product safety and confirm no microbial contamination during drug product manufacturing process, microbial examination will be tested at the beginning and end of stability study to the acceptance criteria established per harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 for the first three commercial and annual commitment lots of drug product.

Reviewer's Assessment: Adequate

Even though the applicant stated that full microbial test for the drug product is unnecessary they still committed to perform the full microbial test per USP <1111>. This is adequate.

2.3.P.7 Container/Closure System

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

Reviewer's Assessment: N/A

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

29. 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)?

Reviewer's Assessment: N/A

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

Applicant's Response:

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Recommended for approval from microbiology perspective

Ying Wang 11/2/2015

Secondary Review Comments and Concurrence:

I concur.

Upinder Atwal, Ph.D.
Branch Chief (Acting)
DPA I / Branch III

11/09/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

31. Is the applicant's claim for categorical exclusion acceptable?
32. Is the applicant's Environmental Assessment adequate for approval of the application?

The applicant requests a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the concentration of emtricitabine and tenofovir alafenamide in the aquatic environment is expected to be less than 1 part per billion. This is based on the estimated annual production over the next five years, and considers all Gilead products containing these active ingredients. To the best of Gilead's knowledge, no extraordinary circumstances exist for this product which may significantly affect the quality of the human environment.

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

From the drug product perspective this application is recommended for approval.

Shrikant Pagay, Ph.D. Dec 14, 2015

DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Pagay's recommendation.

Stephen Miller, Ph.D. Dec 15, 2015

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

Labeling & Package Insert

1. Package Insert

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

DESCOVY™ (emtricitabine and tenofovir alafenamide) tablets, for oral use

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Establishment names are included	Proprietary name is pending
Dosage form, route of administration	yes	
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	yes	

Conclusion: : Satisfactory

The product name, dosage form and strength are accurately presented in the package insert. The short names FTC for emtricitabine and TAF for tenofovir alafenamide are linked under "Indications and Usage" section of the highlights.

(b) “Full Prescribing Information” Section**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

Tablets:

- 200 mg/25 mg: 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate) - blue, rectangular-shaped, film-coated debossed with “GSI” on one side and “225” on the other side

(b) (4)

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

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

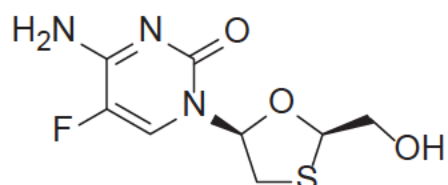
DESCOVY (emtricitabine and tenofovir alafenamide) is a fixed-dose combination tablet containing emtricitabine (FTC) and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV-1 NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

Each 200/25 mg tablet contains 200 mg of FTC and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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

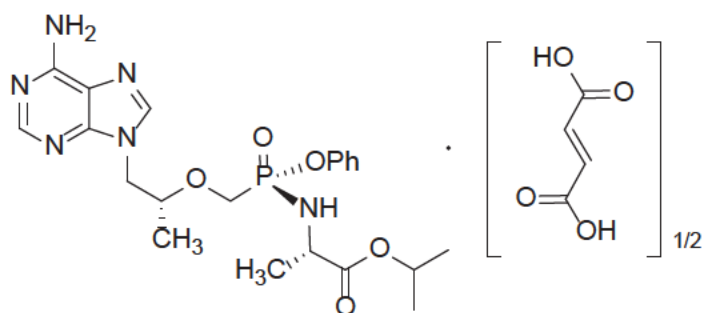
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 and has the following structural formula:



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

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).

Tenofovir alafenamide fumarate 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 and 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
Proprietary name and established name	Established name provided	
Dosage form and route of administration	yes	
Active moiety expression of strength with equivalence statement for salt (if applicable)	yes	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	yes	Labeling reviewer has already recommended listing in alphabetical order.
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	No; provided in other section	Labeling reviewer has included therapeutic class
Chemical name, structural formula, molecular weight	yes	
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	yes	

Conclusion : satisfactory. Comment for consideration during labeling:
Within the parts of Section 11 where the tablet composition and nature of the drug substances are described we recommend that full names be used rather than the acronyms, FTC and TAF.

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

DESCOVY 200 mg/25 mg tablets are blue, rectangular-shaped, and film-coated with "GSI" debossed on one side and "225" on the other side. Each bottle contains 30 tablets (NDC 61958-2002-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

(b) (4)

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	yes	
Available units (e.g., bottles of 100 tablets)	yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	yes	
Special handling (e.g., protect from light, do not freeze)	yes	
Storage conditions	yes	

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

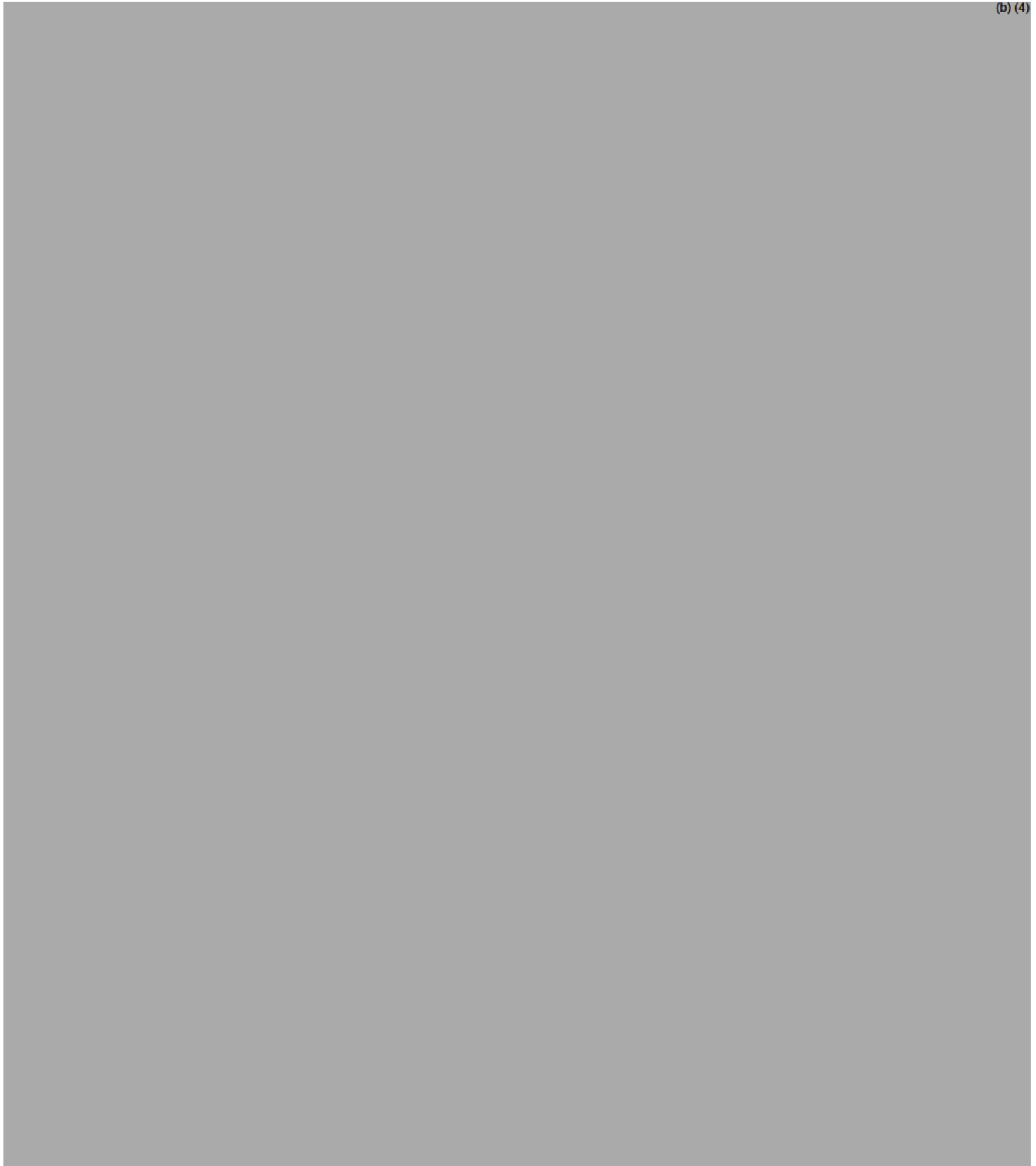
Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	yes	

Conclusion: Satisfactory Comments for consideration during labeling:

We note that the list of active ingredients in the Patient Information section includes the counterion (tenofovir alafenamide fumarate), which was not the case for the Genvoya tablet. From the Prod Qual perspective, it seems preferable to omit "fumarate" except when describing the drug substance (as in one part of Section 11).

2. Container and Carton Labeling

1) Immediate 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))	Font size of proprietary name may be too large. Check for font size to comply with regs.	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	yes	
Route of administration (21.CFR 201.100(b)(3))	Not required for oral drug products	
Net contents* (21 CFR 201.51(a))	yes	
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
"Rx only" statement per 21 CFR 201.100(b)(1)	yes	
Storage (not required)	yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	
Bar Code per 21 CFR 201.25(c)(2)***	yes	
Name of manufacturer/distributor (21 CFR 201.1)	yes	
Others	Note to Pharmacist: Do not cover the alert warning	

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

****Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.**

**Conclusion:
Satisfactory**

2) Carton Labeling

(b) (4)

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))	yes	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	yes	
Net contents (21 CFR 201.51(a))	yes	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	NA	
Sterility Information (if applicable)	NA	
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	yes	
Storage Conditions	yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	
Bar Code per 21 CFR 201.25(c)(2)**	yes	
Name of manufacturer/distributor	yes	
“See package insert for dosage information” (21 CFR 201.55)	yes	
“Keep out of reach of children” (optional for Rx, required for OTC)	??	
Route of Administration (not	NA	

required for oral, 21 CFR
201.100(d)(1) and (d)(2))

Conclusion: Satisfactory. Comment for consideration during labeling:

At an appropriate time, please submit container/carton labels for both the US and Access products with "Tradename" replaced as appropriate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The current labeling is adequate for approval, and recommendations for consideration as labeling is finalized have been included in the executive summary section.

Shrikant Pagay, Ph.D. Dec 14, 2015
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Pagay's recommendation.

Stephen Miller, Ph.D. Dec 15, 2015
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ

II. List of Deficiencies To Be Communicated

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

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

(b) (1) (A)

Recommendation pending at this time

NDA 208215 Review #1

Drug Name/Dosage Form	Emtricitabine and Tenofovir Alafenamide
Strength	200mg/25mg and (b) (4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Orig	04/07/15	Product Quality
Amendment	06/12/15	Product Quality
Amendment	07/14/15	Product Quality
Amendment	08/06/15	Product Quality
Amendment	09/04/15	Product Quality
Amendment	12/08/15	Product Quality

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker, PhD	OPQ/ONDP/NDAP/Branch I
Drug Product	Shrikant (Suresh) Pagay, PhD	OPQ/ONDP/NDPI/Branch III
Process	Ying Wang, PhD	OPQ/OPF/DIV-1/BRANCH-III
Microbiology	Ying Wang, PhD	OPQ/OPF/DIV-1/BRANCH-III
Facility	Frank Wackes	OPQ/OPF/DIA/Branch II
Biopharmaceutics	Gerlie Gieser, PhD	OPQ/ONDP/DB/Branch I
Regulatory Business Process Manager	Maryam Changi, PharmD	OPRO/Div I/ Branch-I
Application Technical Lead	Stephen Miller, PhD	OPQ/ONDP/NDPI/Branch III
ORA Lead	Paul Perdue, PhD	ORA/OMPTO/MIN-DO

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS ***
	(b) (4)					
(b) (4)				Adequate	11/9/2012	
				Adequate	5/29/2014	
				Adequate	4/24/2012	
				Adequate	10/25/2012	
				Adequate	9/10/2012	
				Reviewed Madurawe	12/7/2004	
				Adequate	1/27/2014	
				--	--	
				Adequate	10/24/2012	
				--	--	
				Adequate	10/4/2013	
				Adequate	8/14/2014	
				Reviewed Puttagunta	6/7/2005	
				Adequate	8/19/2014	
				Adequate	3/21/2012	
				Adequate	9/18/2014	
				--	--	
				--	--	

	(b) (4)	—	—	
		—	—	

*****Comment:**

Type III and Type IV DMFs: Adequate information is provided in the NDA and reviewed under appropriate sections.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	111851	IND for this product
NDA	208351	Related product (emtricitabine, rilpivirine and TAF) currently also under NDA review
NDA	207561	Only approved NDA for a product containing TAF (in a 4-drug combination tablet)

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Environmental Assessment	NA	James Laurenson provided advice regarding the Categorical Exclusion statements for several TAF-containing NDAs.		

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the quality of the drug substances and this drug product. However, at this time the assessment of the manufacturing facilities is not yet complete.

NDA 208215 cannot be recommended for approval until the assessment of the (b) (4) facility is finalized.

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

1. Summary of Complete Response issues NA
2. Action letter language, related to critical issues such as expiration date
We also acknowledge receipt of information related to DESCovy® (emtricitabine and tenofovir alafenamide), 200/25 mg (b) (4) fixed-dose combination tablet for your Gilead Access Program that was reviewed as part of this application.
3. Benefit/Risk Considerations
Evaluation of the quality aspects of Descovy tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

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

II. Summary of Quality Assessments

A. Drug Substance [Tenofovir Alafenamide Fumarate] Quality Summary

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

(b) (4) Note that a lower dose of TAF fumarate (10mg/day) is used for treatment regimens that include a PK booster (such as the Genvoya tablet, (b) (4)

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

A. Drug Substance [Emtricitabine] Quality Summary

See NDA 21752 and detailed review notes, below.

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

- a. Strength: 200mg/25mg (b) (4)
- b. Description/Commercial Image of US Product:
200/25 mg tablets are blue, rectangular-shaped, film-coated tablets with “GST” debossed on one side and “225” on the other side.

(b) (4)

Description/Commercial Image of Access Product:

Identical except that the film coats are white, and the second sides are debossed “A25” (b) (4) for the 200/25mg (b) (4)

- c. Summary of Product Design: The product is a monolithic tablet with two drug substances, and is produced using conventional pharmaceutical processes. The specification includes tests for appearance, identity, water, assay, degradants, uniformity, dissolution, and microbial limits. The specification is largely conventional for an immediate release solid oral dosage form and a satisfactory justification is provided. The limit for (b) (4) was reduced from NMT (b) (4) % to NMT (b) (4) % to reduce the risk of TAF-associated degradants exceeding their acceptance criteria on storage. The degradants are toxicologically qualified at the proposed limits. The analytical methods are described in reasonable detail and have been validated and shown to be reasonably robust. Satisfactory batch analyses are provided for 5 batches of each strength. Four of these batches are (b) (4). Also, satisfactory batch analyses are provided for 3 batches of (b) (4) of the Access tablet; the batch size of Access tablets is (b) (4) per batch.
- d. List of Excipients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and indigo carmine aluminum lake (200/25mg) (b) (4). The magnesium stearate (b) (4).
- e. Process Selection (Unit Operations Summary):

(b) (4)

- f. **Container Closure:** The tablets are packaged in HDPE bottles containing 30 tablets, a silica gel desiccant, polyester coil, and closed with a child-resistant closure.
- g. **Expiration Date & Storage Condition:** The applicant claims a 24 month expiration dating period with the storage statement: "Store below 30°C". This is supported with a statistical analysis of the available stability data, including the 30°C/75% RH long-term data, and is acceptable.
- h. Twelve months of satisfactory stability data are provided for three batches stored at 25°C/60% RH and 30°C/75% RH as well as 6 months stored at 40°C/75% RH. There are no out of specification results. The only obvious trends are an increase in TAF impurities (b) (4) and total TAF impurities with time and temperature. The stability behavior of the US and Access tablets are the same .
- i. **List of Co-Packaged Components:** None

C. Summary of Drug Product Intended Use

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

D. Biopharmaceutics Considerations

a) BCS Designation:

- Drug Substance: No official designation has been requested in this application. (b) (4)
- Drug Product: (b) (4)

b) Biowaivers/Biostudies

- Biowaiver Requests:—N/A
- PK studies(pivotal BA/BE Studies): GS-US-311-1472 and GS-US-311-1473
- IVIVC: N/A

E. Novel Approaches**F. Any Special Product Quality Labeling Recommendations**

a) (suggested text edits for OCP reviewer consideration) **Section 12.3**

Pharmacokinetics:

In single-dose crossover studies involving healthy subjects who received test and reference treatments with a moderate-fat, moderate calorie breakfast, the plasma AUC and Cmax of emtricitabine (FTC) and tenofovir alafenamide (TAF) were comparable between DESCOVY® (F/TAF) 200/25 mg fixed dose combination tablet and GENVOYA® EVG/COBI/FTC/TAF (150/150/200/10 mg) fixed-dose combination tablet, and between DESCOVY® 200/10 mg (coadministered with EVG 150 mg and COBI 150 mg) and GENVOYA®.

(b) (4)

Additional labeling recommendations

- a. Within the parts of Section 11 where the tablet composition and nature of the drug substances are described we recommend that full names be used rather than the acronyms, FTC and TAF.
- b. We note that the list of active ingredients in the Patient Information section includes (b) (4) which was not the case for the Genvoya tablet. From the Prod Qual perspective, it seems preferable to omit (b) (4) except when describing the drug substance (as in one part of Section 11).
- c. At an appropriate time, please submit container/carton labels for both the US and Access products with "Tradename" replaced as appropriate.

G. Life Cycle Knowledge Information (see Attachment A)**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY**

Application Technical Lead Signature:

NDA 208215 cannot be recommended for approval until the assessment of the Patheon facility is finalized.

Stephen
Miller -S

 Digitally signed by Stephen Miller -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Stephen Miller -S,
0.9.2342.19200300.100.1.1=1300087013
Date: 2015.12.18 16:14:20 -05'00'

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

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES**Reviewer's Assessment and Signature:**

All facility evaluations are complete and acceptable, except for the drug product manufacturer: Patheon Inc – Toronto (FEI 3000264888). A PAI was performed on November 9-13, 2015 and the review of this inspection is pending finalization. An FDA 483 was issued but did not include any product specific observation. The field investigators classified the inspection as VAI and recommended approval of NDA 208215.

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

Frank Wackes 12/16/2015

Secondary Review Comments and Concurrence:

I concur with the pending assessment. An addendum review with the final Facility Review recommendation is required.

Christina Capacci-Daniel, PhD – Dec 16, 2015
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This Biopharmaceutics assessment is focused on the evaluation of the following:

1. the proposed dissolution method,
2. the proposed dissolution acceptance criteria, and
3. the three BA/BE studies.

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

Yes.

The in vitro dissolution test is part of the QC specifications for the proposed product's release and stability testing. The proposed dissolution test and the revised acceptance criterion ($Q = \frac{(b)}{(4)}\%$ at 30 minutes) are adequate.

Dissolution method:

The proposed dissolution method for emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) fixed dose combination (FDC) product is summarized below.

USP Apparatus II (paddle), operated at 75 rpm
Dissolution medium: 500 mL 50 mM sodium citrate buffer,
pH 5.5, 37 °C

Given that both FTC and TAF are highly soluble, the dissolution medium volume selected was 500 mL (lower limit of the range recommended for Apparatus II). Compared to $\frac{(b)}{(4)}$ rpm, a paddle speed of 75 rpm ensured complete dissolution within 30 minutes, and lower variability. The dissolution of FTC and TAF was equivalent in the medium with and without deaeration.

The Applicant claims that the proposed dissolution method is appropriate as a quality control test

(b) (1) (A)

(b) (1) (A)

(b) (4)

(b) (4)

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immediately following this
page

Reviewer's Assessment:***Dissolution Method***

The reviewer agrees with the Applicant that the dissolution method proposed for QC release and stability testing of the two strengths of the FTC/TAF FDC tablet is discriminating, while maintaining TAF stability in solution.

The proposed dissolution method is a suitable quality assurance test of batch-to-batch consistency (b) (1) (A)

(b) (1) (A)

Dissolution acceptance criterion:

The Applicant's proposed dissolution acceptance criteria are:

- (b) (4)
- FTC/TAF 200/25 mg tablets: Q = 75% for the amount of FTC and TAF dissolved at 30 minutes

Per ICH Q6A Decision Tree 7, a single point acceptance criterion with a lower limit is acceptable. The proposed dissolution acceptance criteria are based on the dissolution results (Figure 38-1) from clinical and development batches of FTC/TAF tablets. (b) (4)

Reviewer's Assessment:***Dissolution Acceptance Criteria***

In general, the dissolution acceptance criteria should be based on the time point where at least (b) (4) % (Q) dissolution is achieved. Note that Lots CR1308B (b) (4) 200/25 mg tablets, respectively) were shown to be bioequivalent to reference treatment in all three BA/BE Studies conducted by the sponsor. At the time of lot release, these (b) (4) lots showed (b) (4) % dissolution in (b) (4) minutes (Table 38-1).

Table 38-1. Summary of In Vitro Dissolution Profiles of FTC and TAF from Descovy® (FTC/TAF) 200/10 mg Tablets (CR1308B) and FTC/TAF 200/25 mg Tablets (CR1305B) used in Pivotal Bioequivalence Studies (b) (4) GS-1473

(b) (4)

(b) (4)

(b) (4)

This recommendation was communicated in an information request dated 8/30/2015. The Applicant responded on 9/4/2015, and agreed to the FDA recommendation to use $Q = \frac{(b)(4)}{(4)}\%$ within 30 minutes as the dissolution acceptance criterion for the 200/25 mg strength tablet. As requested by the FDA, revised Drug Product specification tables were included in the Applicant's response.

Relative Bioavailability Studies:

To evaluate relative bioavailability, three single-dose, crossover studies involving healthy subjects who received test and reference treatments with a moderate-fat, moderate-calorie breakfast were conducted.

Comparable bioavailability of FTC/TAF FDC tablet strengths 200/25 mg (unboosted) (b) (4) to reference treatment (either E/C/FTC/TAF 150/150/200/10 mg FDC tablet or FTC 200mg capsule + TAF 25 mg tablet) was established in clinical studies (Table 38-2 to Table 38-4). FTC and TAF are highly soluble compounds (i.e., BCS-1 and BCS-3, respectively). In vitro-in vivo correlation (IVIVC) for FTC and TAF is not expected for this *immediate-release* FDC tablet.

Table 38-2. Study GS-US-311-1473: Sponsor's Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Set)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC _{last} (ng•h/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32 (96.48, 104.31)
AUC _{inf} (ng•h/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54 (94.61, 102.62)
C _{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63 (95.46, 112.49)
FTC PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC _{last} (ng•h/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01 (88.88, 91.16)
AUC _{inf} (ng•h/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20 (89.06, 91.35)
C _{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26 (94.57, 100.03)

Source: m5.3.1.2, GS-US-311-1473, Section 15.1, Tables 4.2.1, 4.2.2, 5.1, 5.3.1, and 5.3.2

Adapted from NDA 208-215, Clinical Summary 2.7.1, Table 15
F = FTC; TAF (as free base)

(b) (4)

Table 38-4. Study GS-US-311-1088: Sponsor's Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Set)

	Mean (%CV) by Treatment		GLSM Ratio (90% CI), %
	F/TAF (Test) (N = 55)	FTC+TAF (Reference) (N = 55)	
TAF PK Parameter			
AUC _{last} (ng•h/mL)	265.1 (42.9)	253.6 (33.7)	102.68 (95.78, 110.09)
AUC _{inf} (ng•h/mL)	273.8 (45.4) ^a	257.9 (34.4) ^b	105.77 (97.26, 115.01)
C _{max} (ng/mL)	232.4 (51.9)	248.1 (44.7)	92.59 (82.31, 104.16)
FTC PK Parameter			
AUC _{last} (ng•h/mL)	9175.8 (17.4)	9596.0 (22.9)	96.16 (94.29, 98.08)
AUC _{inf} (ng•h/mL)	9387.7 (17.3)	9821.6 (22.5)	96.09 (94.24, 97.96)
C _{max} (ng/mL)	1873.5 (27.2)	1767.6 (22.8)	104.98 (100.75, 109.39)

a n = 43

b n = 48

Source: m5.3.1.2, GS-US-311-1088, Section 15.1, Tables 5.1, 5.2, and 6.1

Adapted from NDA 208-215, Clinical Summary 2.7.1, Table 16

F = FTC; ; TAF (as free base)

Reviewer's Assessment:

Relative Bioavailability of DESCOVY® (FTC/TAF) FDC tablets versus GENVOYA® (E/C/FTC/TAF) FDC tablet

Based on the reviewer's confirmatory analyses, the plasma AUC and C_{max} of both FTC and TAF (as free base) achieved with the lot of [REDACTED] (b) (4) and the lot of DESCOVY 200/25 mg (unboosted) [REDACTED] (b) (4) [REDACTED] GS-US-311-1473, respectively, were within pre-specified bioequivalence acceptance limits, as compared to one of the lots of GENVOYA® (EVG/COBI/FTC/TAF 150/150/200/10 mg) FDC tablet evaluated in clinical efficacy trials (see Table 38-5). Additionally, in Study GS-US-311-1088, the lot of the DESCOVY 200/25 mg tablet (the same as that tested in Study 1473) had FTC and TAF bioavailability comparable to that of combination treatment with EMTRIVA (FTC) 200 mg capsule and TAF 25 mg tablet.

(b) (4)

GS-US-311-1473 (n=83 ^c)	Test: FTC/TAF (200/25 mg) FDC tablet [Lot CR1305B2]; unboosted Reference: E/C/FTC/TAF (150/150/200/10 mg) FDC tablet [Lot CP1310B1]	FTC	90.18 (88.87-91.51)	90.03 (88.73-91.35)	96.14 (93.51-98.83)
		TAF	98.13 (94.17-102.25)	98.19 (94.19-102.35)	98.32 (90.17-107.21)
GS-US-311-1088 (n=38 ^c)	Test: FTC/TAF (200/25 mg) FDC tablet [Lot CR1305B2]; unboosted Reference: FTC 200 mg capsule + TAF 25 mg tablet	FTC	93.76 (91.69-95.88)	94.08 (91.92-96.30)	104.82 (99.97-109.90)
		TAF	107.07 (98.02-116.95)	107.18 (98.12-117.09)	95.72 (82.53-111.01)

^a "Bioequivalence" of FTC and TAF in the FTC/TAF FDC to the FTC and TAF components in E/C/FTC/TAF FDC was concluded if the 90% CI of the GLSM ratio of the PK parameters for each analyte between 2 formulations fell within the prespecified bioequivalence boundary of 80% to 125%.

^b F or FTC (emtricitabine); TAF (tenofovir alafenamide; TAF (as free base)); COBI or C (cobicistat); EVG or E (elvitegravir); FDC (fixed dose combination)

^c Reviewer's confirmatory analyses: using Phoenix 6.4 software; includes only the subset of subjects with a complete set of emtricitabine (FTC) and TAF plasma AUCinf, AUClast, Cmax and Tmax

^d For completeness, table includes the "BE" analysis for the COBI and EVG analytes.

Therefore, this Reviewer concludes that (b) (4)
the proposed FTC/TAF 200/25 mg FDC tablet have comparable bioavailability to the reference E/C/FTC/TAF 150/150/200/10 mg FDC tablet which was evaluated in clinical efficacy trials.

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

(b) (4)

Reviewer's Assessment:

The reviewer concurs with the Applicant's assessment that a bridging study between clinical research formulations and the proposed US commercial product is not needed, since the US Presentation tablet formulations tested in the pivotal BA/BE studies are identical to the ones intended for commercialization.

As shown in Figure 38-1 above, the dissolution rates of FTC and TAF (b) (4)

(b) (4)

In response to a FDA information request, the Applicant provided the dissolution profiles for additional lots of Access tablets, and provided clarification regarding the

(b) (4)

(b) (4)

(b) (4) in US Presentation Tablets and Access Tablets

(b) (4)

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS****Reviewer's Conclusion, Recommendation and Signature:**

- The Applicant's proposed dissolution method for Descovy® (FTC/TAF) 200/25 mg (b) (4) FDC tablets (test conditions shown below) is acceptable.
USP Apparatus II (paddle), operated at 75 rpm
Dissolution medium: 500 mL 50 mM sodium citrate buffer, pH 5.5, 37 °C
- The revised dissolution acceptance criterion of $Q = \frac{(b) (4)}{(4)}\%$ at 30 minutes for (b) (4) of Descovy® tablets is acceptable.
- Based on the reviewer's confirmatory analyses of pivotal BA/BE data, when given as single doses to healthy subjects with a moderate-fat, moderate calorie breakfast, unboosted Descovy® FTC/TAF 200/25 mg FDC tablet [Lot CR1305], (b) (4) are bioequivalent to GENVOYA® (EVG/COBI/FTC/TAF 150/150/200/10 mg) FDC tablet [Lot CP1310B1] previously evaluated in clinical efficacy trials. Alternate trade dress or Access tablets (b) (4) 200/25 mg that were manufactured at (b) (4)

From the Biopharmaceutics perspective, NDA 208-215 for FTC/TAF FDC tablets (b) (4) 200/25 mg is recommended for APPROVAL.

11/5/2015

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer,
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I concur with Dr. Gieser's recommendation and conclusions.

11/5/2015

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

ASSESSMENT OF MICROBIOLOGY

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

Per Applicant, F/TAF tablets are an excellent candidate for reduced microbial testing for product release and stability evaluation (USP <1112>) because F/TAF tablets (b) (4)

Furthermore, F/TAF tablets showed no significant bioburden and absence of indicator organisms at release and after storage at 25 °C/60% RH and 30 °C/75% RH for 12 months, and at 40 °C/75% RH for 6 months. Based on these data, microbiological examination on F/TAF tablets is deemed unnecessary according to ICH Q6A, Decision Tree 8. However, in order to assure drug product safety and confirm no microbial contamination during drug product manufacturing process, microbial examination will be tested at the beginning and end of stability study to the acceptance criteria established per harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 for the first three commercial and annual commitment lots of drug product.

Reviewer's Assessment: Adequate

Even though the applicant stated that full microbial test for the drug product is unnecessary they still committed to perform the full microbial test per USP <1111>. This is adequate.

2.3.P.7 Container/Closure System

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

Reviewer's Assessment: N/A

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

29. 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)?

Reviewer's Assessment: N/A

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

Applicant's Response:

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Recommended for approval from microbiology perspective

Ying Wang 11/2/2015

Secondary Review Comments and Concurrence:

I concur.

Upinder Atwal, Ph.D.
Branch Chief (Acting)
DPA I / Branch III

11/09/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

31. Is the applicant's claim for categorical exclusion acceptable?
32. Is the applicant's Environmental Assessment adequate for approval of the application?

The applicant requests a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the concentration of emtricitabine and tenofovir alafenamide in the aquatic environment is expected to be less than 1 part per billion. This is based on the estimated annual production over the next five years, and considers all Gilead products containing these active ingredients. To the best of Gilead's knowledge, no extraordinary circumstances exist for this product which may significantly affect the quality of the human environment.

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

From the drug product perspective this application is recommended for approval.

Shrikant Pagay, Ph.D. Dec 14, 2015

DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Pagay's recommendation.

Stephen Miller, Ph.D. Dec 15, 2015

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

Labeling & Package Insert

1. Package Insert

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

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Establishment names are included	Proprietary name is pending
Dosage form, route of administration	yes	
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	yes	

Conclusion: : Satisfactory

The product name, dosage form and strength are accurately presented in the package insert. The short names FTC for emtricitabine and TAF for tenofovir alafenamide are linked under "Indications and Usage" section of the highlights.

(b) "Full Prescribing Information" Section

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

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

Conclusion : Satisfactory

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

[TRADENAME] is a fixed dose combination tablet contains FTC and TAF for oral administration.

- FTC is a synthetic nucleoside analog of cytidine. EMTRIVA is the brand name for FTC.
- TAF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

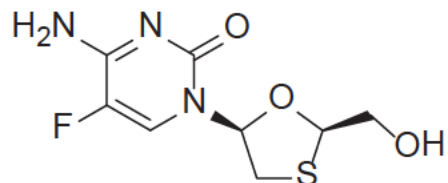
Each 200/25 mg tablet contains 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets include the following inactive ingredients: microcrystalline cellulose, Croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and indigo carmine aluminum lake.

(b) (4)

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

(-)-enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

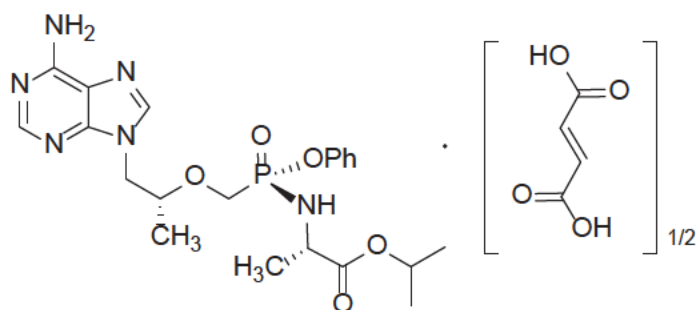
It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



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

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, (*2E*)-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 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	Established name provided	
Dosage form and route of administration	yes	
Active moiety expression of strength with equivalence statement for salt (if applicable)	yes	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	yes	Labeling reviewer has already recommended listing in alphabetical order.
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	No; provided in other section	Labeling reviewer has included therapeutic class
Chemical name, structural formula, molecular weight	yes	
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	yes	

Conclusion : satisfactory. Comment for consideration during labeling:
Within the parts of Section 11 where the tablet composition and nature of the drug substances are described we recommend that full names be used rather than the acronyms, FTC and TAF.

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

[TRADE NAME] 200/25 mg tablets are blue, rectangular-shaped, film-coated tablets with "GSI" debossed on one side and "225" 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.

(b) (4)

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	yes	
Available units (e.g., bottles of 100 tablets)	yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	yes	
Special handling (e.g., protect from light, do not freeze)	yes	
Storage conditions	yes	

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)	yes	

Conclusion: Satisfactory Comments for consideration during labeling:

We note that the list of active ingredients in the Patient Information section includes the counterion (tenofovir alafenamide fumarate), which was not the case for the Genvoya tablet. From the Prod Qual perspective, it seems preferable to omit "fumarate" except when describing the drug substance (as in one part of Section 11).

2. Container and Carton Labeling

1) Immediate Container Label



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))	Font size of proprietary name may be too large. Check for font size to comply with regs.	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	yes	
Route of administration 21.CFR 201.100(b)(3))	Not required for oral drug products	
Net contents* (21 CFR 201.51(a))	yes	
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
“Rx only” statement per 21 CFR 201.100(b)(1)	yes	
Storage (not required)	yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	
Bar Code per 21 CFR 201.25(c)(2)***	yes	
Name of manufacturer/distributor (21 CFR 201.1)	yes	
Others	Note to Pharmacist: Do not cover the alert warning	

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:
Satisfactory

2) Carton Labeling

(b) (4)

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))	yes	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	yes	
Net contents (21 CFR 201.51(a))	yes	
Lot number per 21 CFR 201.18	yes	
Expiration date per 21 CFR 201.17	yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	NA	
Sterility Information (if applicable)	NA	
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	yes	
Storage Conditions	yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	
Bar Code per 21 CFR 201.25(c)(2)**	yes	
Name of manufacturer/distributor	yes	
“See package insert for dosage information” (21 CFR 201.55)	yes	
“Keep out of reach of children” (optional for Rx, required for OTC)	??	
Route of Administration (not	NA	

required for oral, 21 CFR
201.100(d)(1) and (d)(2))

Conclusion: Satisfactory. Comment for consideration during labeling:

At an appropriate time, please submit container/carton labels for both the US and Access products with "Tradename" replaced as appropriate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The current labeling is adequate for approval, and recommendations for consideration as labeling is finalized have been included in the executive summary section.

Shrikant Pagay, Ph.D. Dec 14, 2015
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Pagay's recommendation.

Stephen Miller, Ph.D. Dec 15, 2015
CMC-Lead; Branch-III; DNDP-I; ONDP; OPQ

II. List of Deficiencies To Be Communicated

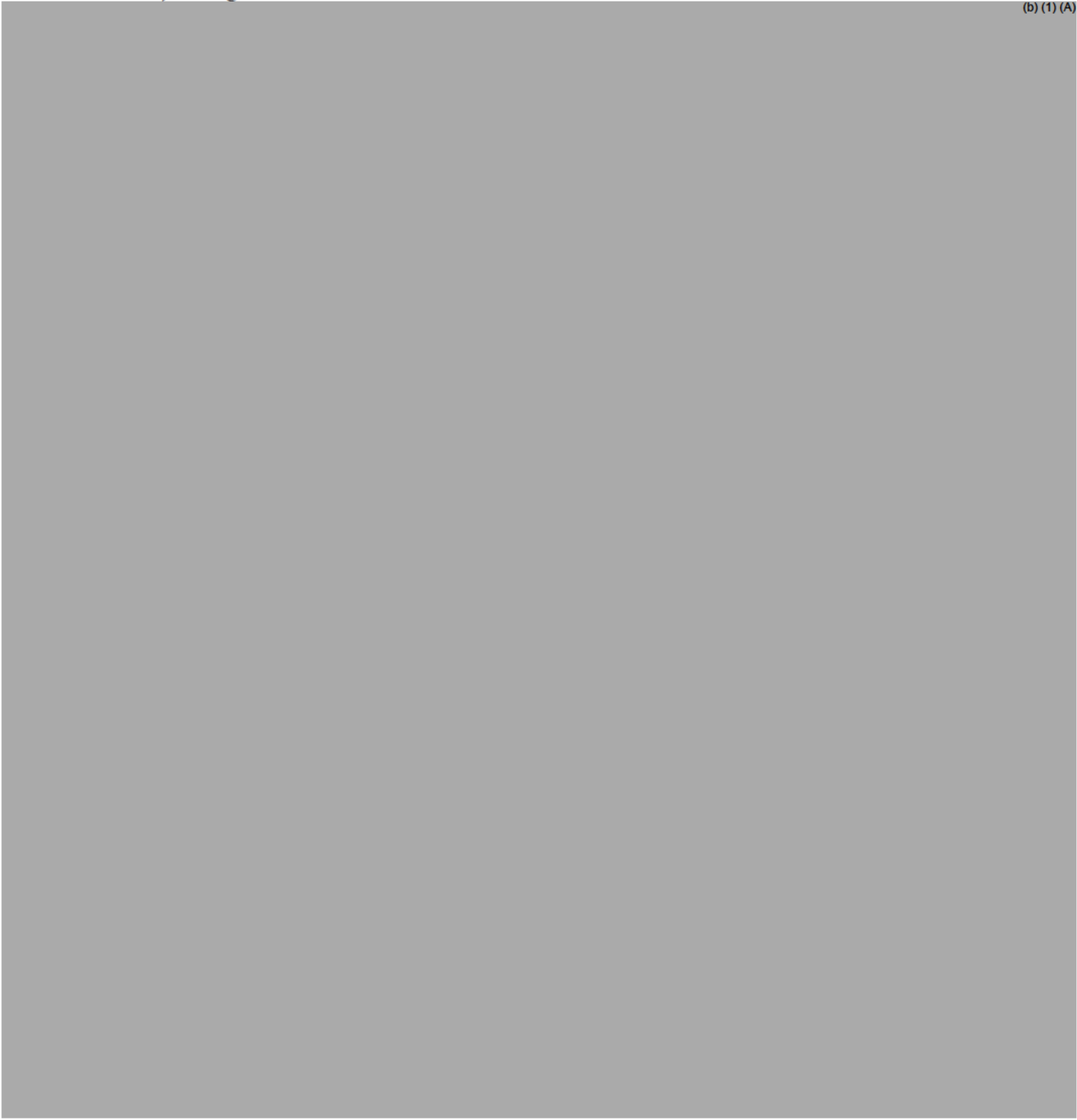
Drug Substance
Drug Product
Process
Facility
Biopharmaceutics
Microbiology
Environmental
Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

(b) (1) (A)



OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208215

Submission Type:
NDA – 505 (b)(1)

Established/Proper Name:
F/TAF (emtricitabine/tenofovir
alafenamide fixed dose
combination); the name
DESCOVY was conditionally
approved under IND 111851

Applicant: GILEAD
SCIENCES INC

Letter Date: April 7, 2015

Dosage Form: Tablets

Chemical Type: 1,4
(NME; new combo)

Stamp Date: April 7, 2015

Strength: 200 mg/25 mg and
(b) (4) tablets

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	Y		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA – recommendation is fileable
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		N	Describe potential review issues here or on additional sheets None identified at this time. Discussed at Kick-Off mtg: 1) Steve will ask the EA team how to address new guidance for NMEs, since TAF fumarate is an NME until approved under 207561. 2) Plan to coordinate container and PI labeling recommendations with 207561

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	Y		
2.	Botanical ¹		N	
3.	Naturally-derived Product		N	
4.	Narrow Therapeutic Index Drug		N	
5.	PET Drug		N	
6.	PEPFAR Drug		N	However, all fully approved drugs eligible for procurement under PEPFAR

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
7.	Sterile Drug Product		N	
8.	Transdermal ¹		N	
9.	Pediatric form/dose ¹		N	
10.	Locally acting drug ¹		N	
11.	Lyophilized product ¹		N	
12.	First generic ¹		N	
13.	Solid dispersion product ¹		N	
14.	Oral disintegrating tablet ¹		N	
15.	Modified release product ¹		N	
16.	Liposome product ¹		N	
17.	Biosimilar product ¹		N	
18.	Combination Product _____		N	Only 2-drug Fixed Dose Combination (FDC) tablet
19.	Other _____			

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	Y		
21.	End of Phase II/Pre-NDA Agreements		N	No specific CMC agreements under IND 111851: - EOP-2 (non-CMC) Oct 2013 - PreNDA (non-CMC) Dec 2014
22.	SPOTS (Special Products On-line Tracking System)		N	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		N	
24.	Comparability Protocol(s) ²		N	
25.	Other _____			
Quality Considerations				
26.	Drug Substance Overage		N	
27.	Design Space	Formulation		N
28.		Process		N
29.		Analytical Methods		N
30.		Other		
31.	Real Time Release Testing (RTRT)		N	
32.	Parametric Release in lieu of Sterility Testing		N	
33.	Alternative Microbiological Test Methods			To be determined as part of NDA review
34.	Process Analytical Technology ¹		N	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product		To be determined as part of NDA review
36.		Excipients		To be determined as part of NDA review
37.		Microbial		To be determined as part of NDA review
38.	Unique analytical methodology ¹			To be determined as part of NDA review
39.	Excipients of Human or Animal Origin		N	
40.	Novel Excipients		N	
41.	Nanomaterials ¹		N	
42.	Hold Times Exceeding 30 Days			(b) (4)
43.	Genotoxic Impurities or Structural Alerts	Y		Controlled via DS process and testing
44.	Continuous Manufacturing		N	
45.	Other unique manufacturing process ¹		N	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		N	
47.	New delivery system or dosage form ¹		N	
48.	Novel BE study designs	☐	☒	
49.	New product design ¹		N	
50.	Other _____			

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	Y			Cat Exclusion: both actives (b) (4) considering all Gilead products (b) (4) for Emtricitabine and (b) (4) for TAF fumarate); no special circumstances.
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ☐ Facilities and Equipment ☐ Adventitious Agents Safety Evaluation ☐ Novel Excipients ☐ Regional Information ☐ Executed Batch Records ☐ Method Validation Package ☐ Comparability Protocols	Y			Organized by CTD sections (non-QbR)
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	Y			Facility information was provided on the 356h dated Apr 8, 2015. The 14 facilities (with 18 responsibilities) were cross-checked with Module 3.
DRUG SUBSTANCE INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?			NA	The drug substance information for both actives are cross-referenced to these Gilead applications: Emtricitabine: is cross-referenced to the approved NDA 21-752 which was recently updated to “provide specific sections that have been requested by the Agency for initial NDA submissions for fixed dose combinations.” (email from K. Schumann, Nov 4, 2014) TAF fumarate: 207561 (currently under review).
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ general information ☐ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	Y			See element 5, directly above

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C. FILING CONSIDERATIONS					
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development - o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots - o Includes complete description of product lots and their uses during development ☐ Manufacture - o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product - o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) - o Includes data to demonstrate process consistency (i.e. data on process validation lots) - o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) - o Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System - o Include data outlined in container closure guidance document ☐ Stability - o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION	Y			Intended Commercial Scale: The batch size for emtricitabine/tenofovir alafenamide (F/TAF) tablets is (b) (4) A manufacturing flow diagram and narrative descriptions are provided, which include in process controls. Primary Stability Data (US presentation): 12 months of long-term stability data (including 30°C/75%RH), plus accelerated data, are provided on 3 batches of each strength (b) (4) Commercial container is HDPE bottle of 30 with desiccant, induction seal and CR closure. Access Tablet: 3 months of of long-term stability data (including 30°C/75%RH), plus accelerated data, are provided on 1 batch of each strength (b) (4)
BIOPHARMACEUTICS					
ATL asked BP reviewer, who agreed to complete elements 8-13 prior to the OPQ Kick-Off meeting.					

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C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☒	☐	☐	• Yes, the NDA includes the clinical study reports, complete supporting analysis datasets and their respective define files for the three comparative BA/BE studies, as well as the Biopharmaceutics Summary. ➤ Yes, the PK files are in the correct format. The PK parameter and plasma concentration data tabulation and analysis datasets are in the acceptable (.xpt) format. ➤ The bioanalytical sample analysis and method validation reports were submitted. • Yes, an inspection request was submitted on 01 May 2015 for the clinical and analytical sites of the (b) (4) pivotal BE studies (b) (4) and GS-US-311-1473. The Applicant has provided the complete clinical site information.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? (Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)	☐	☐	☒	• The to-be-marketed F/TAF FDC tablet has (b) (1) (A) (b) (4) GS-US-311-1473), in the Phase 3 PK/tolerability study in HIV patients (GS-US-311-1089), and in registration stability batches. There were no in vitro or in vivo bridging studies conducted between the proposed commercial/BE/stability formulation and the initial Phase 1 formulation (evaluated in DDI Study GS-US-311-0101 with COBI-boosted DRV). Additional bridging is not needed.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	This NDA does not contain a biowaiver request, because <i>in vivo</i> comparative BA/BE studies were conducted between the two proposed commercial strengths, i.e., 200/25 mg (unboosted), (b) (4) (b) (4) f the to-be-marketed (b) (4) product and the reference product (GENVOYA® E/C/F/TAF 150/150/200/10 mg; NDA 207561 in house).
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	The proposed FDC is an IR drug product.

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12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	The proposed FDC is an IR drug product.
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	No, an official claim or request for BCS-I designation was not submitted. Based on data available, F (emtricitabine) is (b) (1) (A) For F: The dose volume for 200 mg is (b) (1) (A) s the physiologic range; the oral BA of F is (b) (4) in humans. For TAF: The dose volumes for (b) (4) 25 mg are (b) (4) (b) (1) (A), respectively across the physiological pH range; there (b) (4) Dissolution: $\geq$ (b) (4) % in 30 min for (b) (1) (A) F and TAF [see 3.2.P.5.2 for the method development report, 3.2.P.5.3 for the validation report, 3.2.P.5.6 for specifications justification, 3.2.P.2 for effect of processes on dissolution] Stability: TAF (b) (4)
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			NA	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	Y			None for drug substance (b) (1) (A)
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures			NA	

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C. FILING CONSIDERATIONS					
	○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ☐ novel excipients				
17.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			NA	

Summary for Initial Risk Evaluation:

Use by Patients: One tablet per day in combination with other antiretroviral drugs for treatment of HIV infection in adults and pediatric patients 12 years of age and older. (b) (4)

Drug substances:

- Tenofovir Alafenamide Fumarate: high solubility (BCS) across pH range at 25 mg/tablet (85 mg/mL at pH 2, dropping to 4 mg/mL at pH 8); (b) (4)
- Emtricitabine: high solubility (BCS) across pH range at 200 mg/tablet. (b) (4)

Stability:

-
-
-

Fo

Process:

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- [REDACTED] (b) (4)

- [REDACTED] (b) (4)

Container closure system:

- o HDPE bottle of 30 tablets with desiccant [REDACTED] (b) (4) silica gel), polyester coil, induction seal; CR cap.

Biopharmaceutics:

- The Biopharmaceutics Review of this NDA is focused on the evaluation of the acceptability of:
 - 1.The proposed dissolution method,
 - 2.The proposed dissolution acceptance criteria
 - 3.The three BE studies

- Dissolution::

- The proposed commercial *in vitro* dissolution method (for release and stability) is: USP <711> Apparatus II (Paddle), 75 rpm, 500mL of 50 mM sodium citrate pH 5.5 medium at

[REDACTED] (b) (4)

- Disintegration:

- [REDACTED] (b) (4)
- [REDACTED]

- The Biopharmaceutics review of this NDA will evaluate the pivotal BE Studies [REDACTED] (b) (4) [REDACTED] GS-US-311-1473, as well as BE Study GS-US-311-1088; all 3 studies were

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conducted in healthy subjects under fed conditions using the to-be-marketed formulation. (Clinical Pharmacology will review the food-effect and drug-drug interaction studies conducted with the proposed commercial F/TAF FDC tablet.) Per Pre-NDA and EOP2 meeting agreements with FDA:

- (1) Two pivotal BE (Studies GS-US- 311-1472 and Study GS-US-311-1473) were conducted to bridge the proposed F/TAF FDC tablet to the reference product (E/C/F/TAF FDC tablet) with available safety and efficacy data.
 - (2) TFV plasma concentrations were not measured in these BE studies, in addition to F and TAF concentrations.
 - (3) E and C plasma concentrations for the [REDACTED] (b) (4) for the reference arm of Study 1473 were reported.
 - (4) BE was established if the [REDACTED] (b) (4)
 - (5) It appears that BE Study GS-US-311-1088 was not considered pivotal because there was insufficient efficacy to support the use of unboosted TAF.
- Though included in the Biopharmaceutics module, the clinical study report of Study GS-US-299-0101 will not be reviewed because it evaluated a D/C/F/TAF (not the F/TAF) FDC formulation.
 - In addition, comparative BA Study GS-US-311-0101 will not be reviewed [REDACTED] (b) (4)
 - BE inspection is already requested for the clinical and analytical sites of the two pivotal BE studies.

***No Biopharmaceutics comments for the 74-day letter**

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Initial Risk Table for Emtricitabine and Tenofovir Alafenamide Fumarate Tablets (NDA 208-215)

PRODUCT PROPERTY/IMPACT OF CHANGE/COAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Comment
Assay, Stability					(b) (1) (A)
Physical stability (solid state)					
Content uniformity					
Microbial limits					
Dissolution – BCS					
(b) (1) (A)					
(b) (1) (A)					
(b) (1) (A)					
Drug Product Impurity Control					
Patient Use Issues					
Risk to patients associated with product quality issues for similar products from this Applicant					

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

5 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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“This NDA is recommended for filing from the Quality perspective.”

Stephen
Miller -S

 Digitally signed by Stephen Miller S
DN: c=US, ou=U.S. Government, ou=HHS, ou=FDA, ou=People
cn=Stephen Miller S 0 9 2342 19200300 100 1 1=1300087013
Date: 2015.06.01 17:43:54 -0400

Stephen Miller, Ph.D.
CMC-Lead and ATL for NDA 208-215