CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210251Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 210251

Review #2

Drug Name/Dosage Form	Biktarvy (Bictegravir, Emtricitabine, and Tenofovir Alafenamide) tablets
Strength	50 mg Bictegravir / 200 mg Emtricitabine / 25 mg Tenofovir Alafenamide
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED		DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New NDA	SD #0000	*12-Jun-2017*	All
Proprietary Name Review	SD #0001	*20-Jun-2017*	All
Quality Response to IR	SD #0007	*3-Aug-2017*	Drug Substance
Quality Response to IR	SD #0008	*22-Aug-2017*	Biopharmaceutics
Quality Response to IR	SD #0012	*28-Sep-2017*	Drug Substance
Quality Response to IR	SD #0014	*6-Oct-2017*	Biopharmaceutics, Drug Product, and EA
Quality Response to IR	SD #0016	*19-Oct-2017*	Drug Substance and Laboratory
Labeling	SD #0017	*1-Nov-2017*	Drug Product
Quality Response to IR	SD #0019	*27-Nov-2017*	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
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Drug Product	Dr. Yong Wang	Dr. Balajee Shanmugam
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Application Technical Lead	Dr. Andrei Ponta	-

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
NA	Type II	-	-	-	-	-
Various	Type III *(if applicable)*	Various	(b) (4)	Adequate	See DP review	-
Various	Type IV *(if applicable)*	Various		Adequate	See DP review	-
NA	Other	-	-	-	-	-

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
#0000 #0627	NDA 21752	Emtricitabine drug substance and Environmental Analysis
#0000	NDA 207561	Tenofovir Alafenamide drug subsistence
#0001	IND 53971	Emtricitabine
#0001	NDA 21500	Emtricitabine
#0001	NDA 21896	Emtricitabine
#0001	IND 52849	Viread (Tenofovir)
#0001	IND 51285	Viread (Tenofovir)
#0001	NDA 21356	Viread (Tenofovir)
#0001	IND 103093	Stirbild
#0001	NDA 203100	Stirbild
#0001	NDA 201283	Cobicstat
#0001	NDA 202123	Complera
#0001	NDA 208215	Descovy
#0001	NDA 208351	Odefsey
#0001	IND 06737	TAF
#0001	NDA 208464	Vemlidy
#0001	NDA 208341	Epclusa
#0001	NDA 209195	SOF/VEL/VOX
#0001	(b) (4)	Bictegravir
#0001	IND 125589	B/F/TAF
#0001	IND 06761	Truvada
#0001	IND 111007	Genvoya

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharm/Tox	NA			
CDRH	NA			
Clinical	NA			
Other (Method Verification)	Complete	TM-313 and TM 315 are Acceptable TM-306 and TM-311 are Acceptable with Modification	28-Nov-2017	Dr. Priyanka Chistranshi

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the Product Quality perspective. This document (Review #2) contains the final evaluation of all manufacturing facilities, finalized container labels, the Final Risk Assessment, and the summary of all product quality aspects of the NDA. See Review #1 (20-Nov-17) for details of other product quality evaluations.

II. Summary of Quality Assessments

A. Product Overview

This NDA submission is accompanied by a Tropical Disease Voucher and has been reviewed as a priority review.

The proposed drug product, Biktarvy, is a fixed dose combination (FDC) immediate release tablet containing bictegravir (BIC) 50 mg, emtricitabine (FTC) 200 mg, tenofovir alafenamide (TAF) 25 mg. The drug product is a (b) (4) BIC/FTC/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. The tablets are approximately 15 mm in length and 8 mm in width. The container closure system consists of a 100 mL, white, high-density polyethylene (HDPE) bottle containing 30 tablets.

The drug product is indicated for the treatment of HIV-1 infection in adults who are HIV-1 treatment-naïve or virologically-suppressed with no known mutations associated with resistance to the individual components of the drug product (BIC/FTC/TAF). The administration is one tablet daily with or without food. The drug product is intended for chronic use unless resistance develops.

Proposed Indication(s) including Intended Patient Population	Biktarvy is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen.
Duration of Treatment	One tablet taken once daily with or without food. The drug product is for chronic use unless resistance develops.
Maximum Daily Dose	One tablet (50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide).
Alternative Methods of Administration	Oral use only.

B. Quality Assessment Overview

The proposed drug product, Biktarvy, is a fixed dose combination (FDC) immediate release tablet containing bictegravir (BIC) 50 mg, emtricitabine (FTC) 200 mg, tenofovir alafenamide (TAF) 25 mg.

The BIC drug substance is a new molecular entity (NME). The Applicant considers BIC a BCS 2 drug substance (low solubility/high permeability). (b) (4) [redacted] that is an off-white to yellow solid. The Applicant monitors nine related substances which are controlled at various levels in the drug substance specifications. The proposed acceptance criteria of these impurities have been evaluated by the Pharm./Tox. review team and were found to be acceptable. BIC has been shown to be stable under the long-term studies (12 months) and accelerated conditions (6 months).

The Applicant cross references drug substance information for FTC from NDA 21752 (Truvada®, Gilead), which was approved by the Agency on 2-Aug-2004. The Applicant considers FTC as a BCS 1 drug substance (high permeability/high solubility). (b) (4) [redacted]

The Applicant cross references drug substance information for TAF from NDA 207561 (Genvoya®), which was approved by the Agency on 5-Nov-2015. The Applicant considers TAF as a BCS 3 drug substance (low permeability/high solubility). TAF (b) (4) [redacted]

The drug product is a (b) (4) [redacted] tablet containing the three drug substances and compendial excipients, with film coating (b) (4) [redacted]. (b) (4) [redacted]

The manufacturing process has been extensively developed, adequately described and controlled. Note that the formulation and manufacturing process for (b) (4) [redacted] is identical to that of Gilead's approved product, Descovy (NDA #208215).

The commercial drug product is to be manufactured at two sites: (b) (4) [redacted] and Gilead Sciences Ireland UC. The Applicant has provided release and stability results for drug product batches manufactured at both sites. The addition of the

Gilead Sciences Ireland site is also supported with evidence of comparable *in vitro* dissolution profiles between the test and the reference drug products.

The Applicant has manufactured 14 drug product batches to date, 11 of which were manufactured at the [redacted] (b) (4) site while the remaining three were manufactured at Gilead Sciences Ireland UC. The Applicant has used drug substance batches manufactured from all of the proposed commercial manufacturing sites in the manufacture of the drug product. All drug product batches manufactured to date met the propose release specifications.

Gilead has provided twelve months of stability data for three registration batches manufactured at [redacted] (b) (4) and three months of stability data for three batches manufactured at Gilead Sciences Ireland UC. The majority of parameters remain within specifications with no trend being apparent. The drug product shows little to no variation in BIC and FTC assay. Slight drops in TAF assay (0.3 - 1.6%) have been observed but this is within the proposed specifications. The drop in assay is associated with an increase in impurities but these likewise remain within specifications. Based on the stability data, the proposed shelf life of 24 months is acceptable when stored below 30°C.

The Initial Risk Table identified four aspects as moderate risk: physical stability [redacted] (b) (4) content uniformity; dissolution; and drug product impurity controls.

The physical and chemical compatibility of FTC and TAF have been previously established during development of Genvoya, Descovy, and Odefsey. Formulations containing FTC and TAF in combination have exhibited adequate FTC and TAF chemical stability. The Applicant also provided physical and chemical stability data for BIC tablets demonstrating that the drug substance remains stable.

The risk with content uniformity is mitigated by [redacted] (b) (4) testing per USP <905> on release of the drug product. Additionally, the Applicant has performed [redacted] (b) (4) testing as part of the manufacturing process development.

The dissolution method has been evaluated and was shown to have discriminating power for intentional alterations in the tablet formulation, including being able to detect different forms of BIC. The Applicant has also revised the dissolution acceptance criterion (Q = [redacted] (b) (4) % at 30 minutes) ensuring that the criterion is sufficient to reject aberrant drug product batches.

The risk of drug product impurities is primarily associated with TAF related substances. However, the impurities have been qualified by the Applicant at the proposed limit levels and the stability data to date demonstrates that the drug product remains well within these levels.

The drug product container closure system consists of a 100 mL, white, high-density polyethylene (HDPE) bottle and a continuous thread, child-resistant polypropylene (PP) screw cap lined with an induction-sealed, aluminum foil liner. Each bottle contains 30 tablets [redacted] (b) (4) containing a three gram silica gel desiccant, and polyester coil packing material.

The drug product is also to be available as part of the Gilead access program. The tablets to be part of the access program are identical to the proposed commercial drug product. The only difference is the packaging has [redacted] (b) (4) on the container label.

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All sites are found acceptable upon completion of this review. The Overall Manufacturing Facility Status in Panorama is Approve. For details, see the Facility evaluation within this review (Product Quality Review #2)

The Applicant has submitted claims for categorical exclusion for BIC and TAF per 21 CFR 25.15(a) and 21 CFR 25.31(b). A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment has been submitted for the categorical exclusions, per 21 CFR 25.15(a). Gilead has prepared an environmental analysis for FTC evaluating the potential environmental impact from the use and disposal of this product. Based on the information provided, the Agency is issuing a finding of no significant impact and thus an environmental impact statement will not be prepared.

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendations were conveyed to the OND PM for consideration as the labeling is not yet finalized:

1. In Section 16 How Supplied/Storage and Handling, please add names for manufacturer/distributor per 21 CFR 201.1(h)(5).
2. Per 21 CFR 201.17, confirm if the space is available for lot number and expiration date in the proposed container label.

D. Final Risk Assessment (see Attachment)

Andrei Ponta, Ph.D.

Application Technical Lead for NDA 210251

Date: 10-Jan-2018

Andrei Ponta

Digitally signed by Andrei Ponta
Date: 1/10/2018 03:02:10PM
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ENVIRONMENTAL

IQA Review Guide Reference

R Regional Information

Summary: The applicant submitted claims for categorical exclusion for bictegravir (BIC) and tenofovir alafenamid (TAF) from the requirement to prepare an environmental assessment (EA) under 21 CFR 25.15(a) and 21 CFR 25.31(b). A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment was submitted for the categorical exclusions, per 21 CFR 25.15(a). FDA requested additional information and a correction. Upon review, FDA determined that the applicant cited the appropriate exclusion and provided the required statement of no extraordinary circumstances. The claims and updated supporting information were found to be acceptable. The applicant also submitted an EA for emtricitabine (FTC) under 21 CFR 21.14(a) and 21 CFR 25.40. FDA concluded that (1) the EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment and (2) the proposed action does not appear to significantly affect the environment, and thus a finding of no significant impact (FONSI) has been filed.

Environmental

Initially, the applicant submitted

1. Claims for a categorical exclusion for bictegravir (BIC) and tenofovir alafenamid (TAF) from the requirement to prepare an environmental assessment (EA) under 21 CFR 25.15(a) and 21 CFR 25.31(b) and

2. An EA for emtricitabine (FTC, for 2'-deoxy-5-fluoro-3'-thiacytidine) under 21 CFR 21.14(a) and 21 CFR 25.40.

A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment was submitted for the categorical exclusions, per 21 CFR 25.15(a).

Categorical Exclusions

The claims for a categorical exclusion for BIC and TAF was submitted on the basis of a less than 1 part per billion (ppb) level of expected introduction concentration (EIC) at the point of entry into the aquatic environment. Specifically, the BIC EIC was (b) (4) ppb, and the TAF EIC was (b) (4) ppb.

FDA responded that the claim for an exclusion for TAF might not be acceptable because the active moiety, tenofovir, is the same as that of the previously approved tenofovir disoproxil fumerate (TDF), which currently has an EIC of ≥ 1 ppb and thus does not meet

the < 1 ppb requirement. FDA noted that if there will be an increase in tenofovir use due to approval of this application, with an overall tenofovir EIC of ≥ 1 ppb, then an EA would be required. Alternatively, FDA noted, if there will be no change or a decrease in the use of tenofovir, then a categorical exclusion under 21 CFR 25.31(a) (no increased use) would be appropriate. If an EA is required, FDA stated that the environmental risk assessment (ERA) that the applicant has submitted to the European Medicines Agency (EMA), modified as needed to reflect new information, including the expected environmental concentrations in the US, would appear to be appropriate.

The applicant responded and agreed that a TDF EA submission was provided on January 24, 2012, where the EIC was > 1 ppb and thus greater than the threshold for categorical exclusion under 21 CFR 25.31(a)[sic] based on yearly production estimates of TDF (Section 1.12.14, Environmental Analysis, NDA 021356/SN0673). (FDA assumes that reference to 21 CFR 25.31(a), which address the no-increased-use exclusion, was meant to be 21 CFR 25.31(b), which addresses the 1 ppb exclusion.) Both TDF and TAF are prodrugs of the active moiety, tenofovir, the applicant noted. Specifically, conversion of TDF and TAF *in vivo* makes tenofovir a relevant species for consideration of the EIC.

The applicant then conducted an analysis to determine if tenofovir would indeed exceed the EIC threshold of 1 ppb for a categorical exclusion from both TDF and TAF. The EIC of TDF provided in 2012 was calculated to be (b) (4) ppb based on an annual production estimate of (b) (4) kg/year (Section 1.12.14, Environmental Analysis, NDA 021356/SN0673). However, the applicant notes that TDF's molecular weight of 635.32 g/mol is substantially more than that of tenofovir, 287.21 g/mol, which would result in (b) (4) kg/year for tenofovir. TAF is also a prodrug, with a molecular weight of 534.50 g/mol and an estimated annual production of (b) (4) kg/year (NDA 210251, section 1.12.14, Environmental Analysis). The amount of relative contribution of active tenofovir in TAF thus would be (b) (4) kg/year. The total tenofovir contribution from a combination of TDF and TAF production in turn would be (b) (4) kg/year, and the resulting EIC would be (b) (4) ppb (i.e., < 1 ppb). The applicant also notes that the production of TDF has been declining and for 2017 is estimated at (b) (4) kg/year, which would result in an EIC for tenofovir of (b) (4) ppb. Either way, the categorical exclusion per 21 CFR 25.31(b) for tenofovir would be appropriate.

Environmental Assessment

The EIC for FTC was calculated by the applicant at approximately 1.13 ppb. Because this exceeded the categorical exclusion limit of 1 ppb EIC, the applicant provided a cross reference to the revised FTC EA submitted previously (FTC and TDF, NDA 021752, Section 1.12.14, Environmental Analysis, SN 0627, dated June 2, 2017). This EA began with a Tier 1 and 2 assessment, per FDA guidance, and concluded that Tier 3 testing for chronic toxicity was not needed. Tier 3 data were available, however, and therefore the applicant proceeded with the Tier 3 assessment.

The applicant noted that the majority of FTC (1) will be excreted by patients, (2) is unlikely to bind to sewage solids, and (3) is not readily biodegradable. Thus, a

conservative/protective assumption that would be used is that the EIC, Expected Environmental Concentration (EEC), and Maximum Expected Environmental Concentration (MEEC) for FTC are similar, and thus the EA will use an MEEC of 1.13 ppb (or µg/L).

The effects of FTC on the early life stages of fish was investigated with fathead minnows according to OECD Guideline 210, "Fish, Early-Life Stage Toxicity Test". The lowest-observed-effect concentration (LOEC) was 11 mg/L, and the no-observed-effects concentration (NOEC) was determined to be 6.1 mg/L. Comparing this to the MEEC results in a margin of safety of approximately 5,000.

The effects of FTC on the reproduction of *Daphnia magna* were investigated, according to OECD Guideline 211, "Daphnia magna Reproduction Test". The NOEC for reproduction was determined to be ≥ 110 mg/L, the highest dose, and thus no LOEC could be determined. Comparing this to the MEEC results in a margin of safety of approximately 97,000.

The effects of FTC on the pre-emergent aquatic early life stages of the insect *Chironomus riparius* were investigated, according to OECD Guideline 218, "Sediment Water Chironomid Toxicity Test Using Spiked Sediment". The overall NOEC was determined as ≥ 38 mg/kg-dry weight (dw), the highest dose. Based on EMA guidelines, the applicant converted this NOEC into standard sediment with an organic carbon content of 10%, or 200 mg/kg-dw. Comparing to the calculated sediment concentration derived from the MEEC, or 9.2 µg/kg-dw, results in a margin of safety of approximately 22,000.

Reviewer's Assessment:

Categorical Exclusions

The specific claims for categorical exclusions for the EIC for BIC and the corrected EIC for tenofovir, under 21 CFR 25.31(b), are appropriate for the estimated concentrations. A statement of no extraordinary circumstances, per 21 CFR 25.15(a), was included with the claims.

Given BIC is an NME, FDA conducted additional analysis by utilizing a fish plasma model (FPM; per Nallani et al., 2016 and Huggett et al., 2003) to help screen for aquatic environmental risk. FDA used a therapeutic concentration of 5.1 µg/mL (Table 23, "fasted" food effect, CTD section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods), a predicted log D value of 1.35 (www.chemspider.com), and an environmental concentration of (b) (4). The resulting FPM effects ratio (ER) was 11,800, which is greater than the ratio of 1,000 recommended by Huggett et al., 2003, thus indicating little concern for this substance. In addition, FDA examined an assessment of a claim for categorical exclusion of a previous integrase strand-transfer inhibitor, elvitegravir, for NDA 203100. FDA found that based on a variety of analyses, the EIC of (b) (4) ppb for elvitegravir did not indicate the potential for extraordinary circumstances. While (b) (4) ppb is only about 25% of the EIC for BIC, the margin of safety of toxicity data for elvitegravir was approximately

four orders of magnitude, and thus this difference in concentration is insignificant. Thus, the claim for a categorical exclusion from an EA is acceptable.

Tenofovir is not an NME, and because it had been estimated at > 1 ppb previously, an EA had been conducted. This EA also was conducted under NDA 203100 and resulted in a finding of no significant impact (FONSI). The environmental concentration used in that EA was more than double the current concentration reflected in this claim for a categorical exclusion from an EA. Given the FONSI at the higher concentration, this current concentration also is found to not indicate any potential for extraordinary circumstances. FDA also conducted an FPM analysis for tenofovir as with BIC, in part to further validate FPM. FDA used a therapeutic concentration of 0.21 µg/mL (Table 3, Cmax, CTD section 2.5, Clinical Overview), a predicted log D value of -3.55 (www.chemspider.com), and an environmental concentration of (b) (4) ppb. The resulting FPM ER was 440,000, which is substantially greater than the ratio of 1,000 recommended by Huggett et al., 2003, thus indicating little concern for this substance. Given the results of the EA and FPM, the claim for a categorical exclusion from an EA is acceptable.

Environmental Assessment

The main goals of this review of the FTC EA, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

The EA for FTC contains sufficient information to enable a determination of whether the proposed action may significantly affect the quality of the human environment. The data appear to be accurate and objective. This assessment is considered worst-case because the calculation of the EIC does not take into consideration of (1) metabolism, (2) degradation during wastewater treatment, or (3) dilution, degradation, or removal in surface water. FDA expects that an EEC would be more than an order of magnitude below the EIC, thus adding an order of magnitude to the already substantial margins of safety noted in the assessment. FDA also conducted an FPM analysis as with BIC, in part to further validate FPM. FDA used a therapeutic concentration of 2.1 µg/mL (Table 3, Cmax, CTD section 2.5, Clinical Overview), a predicted log D value of -0.9 (www.chemspider.com), and an environmental concentration of 1.13 ppb. The resulting FPM ER was 53,000, which is substantially greater than the ratio of 1,000 recommended by Huggett et al., 2003, thus indicating little concern for this substance. Given the results of the EA and FPM, FDA agrees that FTC poses no significant environmental risk via this application.

References

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential

impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. Comparison of Measured and Predicted Bioconcentration Estimates of Pharmaceuticals in Fish Plasma and Prediction of Chronic Risk. Bulletin of environmental contamination and toxicology, 96(5), 580-584.

Primary Environmental Reviewer Name and Date: James Laurenson, 10/31/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 11/3/2017

James Laurenson

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Michael Furness

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Finding of No Significant Impact

NDA 210251 Bictegravir, Emtricitabine, Tenofovir Alafenamide (BIC, FTC, TAF) Tablet, 50/200/25 mg

Food and Drug Administration
Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

Gilead Sciences (Gilead) requests approval of NDA 210251 for the treatment of HIV-1 infection. The product is a tablet with BIC, FTC, and TAF in combination in the following doses: 50, 200, and 25 mg, respectively. BIC and TAF have been categorically excluded from an environmental assessment (EA). FTC, along with TAF, forms a nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone.

In support of its application, Gilead prepared an EA for FTC (attached). This EA evaluates the potential environmental impact from the use and disposal of this product. The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and additional information, and has carefully considered the potential environmental impact due to approval of this application. Based on the CDER review of the entirety of this information, FDA has determined that approval of the present application for is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachments: May 25, 2017, Environmental Assessment

SECTION 1.12.14
ENVIRONMENTAL ANALYSIS

EMTRICITABINE

GILEAD SCIENCES, INC.

25 May 2017

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
AR	applied radioactivity
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
CFR	Code of Federal Regulations
DNA	deoxyribonucleic acid
DT_X	disappearance time for an X% reduction
EA	Environmental Assessment
EC_{xx}	XX% effective concentration
FDA	(United States) Food and Drug Administration
FTC	emtricitabine, Emtriva®
hr	hour
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug (Application)
K_d	adsorption coefficient for activated sludge
K_{oc}	adsorption coefficient for organic carbon
K_{ow}	octanol water partition coefficient
LC_{50}	median lethal concentration
L	Liter
MEEC	Maximum Expected Environmental Concentration
mg	Milligram
min	minute
NDA	New Drug Application
NEPA	National Environmental Policy Act
NOEC	no obvserved effect concentration
OECD	Organisation for Economic Co-operation and Development
pKa	acid dissociation constant
POTW	publicly owned treatment works
ppb	part per billion
RCE	Request for Categorical Exclusion
SFO	single first-order
STP	sewage treatment plant
UV	ultraviolet light

1. ENVIRONMENTAL RISK ASSESSMENT

1.1. Date

May 24, 2017

1.2. Name of Applicant/Petitioner

Gilead Sciences, Inc.

1.3. Address

333 Lakeside Drive
Foster City, CA 94404

2. DESCRIPTION OF PROPOSED ACTION

2.1. Requested Approval

Gilead Sciences, Inc. (Gilead) has previously filed and received approval of a New Drug Application (NDA) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emtricitabine (FTC) as a stand-alone medication (NDA#s 021500, and 021896) and in combination with other HIV medications (NDA#s 021937, 202123, 208215, 207561, 208531, 203100, and 021752). As part of the general correspondence for NDA 021752, an updated Environmental Assessment for FTC is being submitted pursuant to 21 CFR part 25 to support a new marketing application for bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) tablet (NDA 210251) {Food & Drug Administration (FDA) 2016}.

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process. FDA's regulations in 21 CFR Part 25 specify that environmental assessments (EAs) must be submitted as part of certain NDAs, abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions (see 21 CFR 25.20), unless the action qualifies for categorical exclusion {Food & Drug Administration (FDA) 2016}.

FTC is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following is submitted according to the requirements under the Food and Drug Administration Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, July, 1998, CMC 6, Revision 1 ("FDA Guidance Document") {U. S. Department of Health and Human Services (DHHS) 1998}. In addition to meeting the FDA Guidance Document requirements Gilead has conducted additional environmental studies as part of their product stewardship of FTC and submits these data pursuant to 21 CFR Part 25 {Food & Drug Administration (FDA) 2016}. Gilead requests continued approval of the use of FTC as requirements under the Guidance and per regulatory requirements for environmental assessment have been met as follows.

2.2. Need for Action

FTC is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination.

2.3. Locations of Use

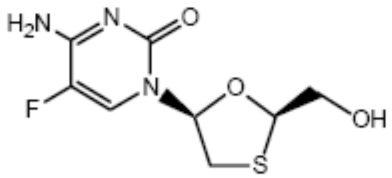
FTC is administered orally and may be used by individuals throughout the United States (US) in hospitals, clinics, and/or homes. It is not expected to be concentrated in any particular geographic region.

2.4. Disposal Sites

In US hospitals, pharmacies or clinics, empty or partially empty bottles will be disposed of according to hospital, pharmacy or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

3. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

3.1. Physical and Chemical Properties

Established Name:	Emtricitabine
Brand/Proprietary Name/ Tradename:	Emtricitabine is used in several brand name products including Stribild®, Odefsey®, Descovy®, Genvoya®, Atripla®, Truvada®, and Emtriva®
Chemical Names:	5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine (IUPAC) 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S* yl)-(1*H*)-pyrimidin-2-one (CAS)
Chemical Abstracts Service (CAS) Registration Number:	143491-57-0
Molecular Formula:	$C_8H_{10}FN_3O_3S$
Molecular Weight:	247.2
Chemical Structure:	

4. ENVIRONMENTAL ISSUES

4.1. Environmental Fate of Released Substances

4.1.1. Identification of Substances of Interest

FTC is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. FTC is minimally transformed (13%), most appears unchanged in urine (86%). The biotransformation of FTC includes oxidation of the thiol moiety to form the 3′-sulfoxide diastereomers (ca. 9% of dose) and conjugation with glucuronic acid to form 2′-O-glucuronide (ca. 4% of dose).

Due to the high proportion of parent excreted, metabolism is considered minimal and not considered further here. A total residue approach is adopted for this risk assessment, where 100% of the dosed FTC is assumed to be excreted unchanged.

The excipients are inert substances which have no pharmacological or toxicological effects and therefore, this assessment will focus on the environmental impact of the active ingredient only.

4.1.2. Physical and Chemical Characterization

The physical and chemical properties of FTC that are environmentally relevant are summarized as follows, and in Appendix 1: Emtricitabine Data Summary Table.

Water Solubility: 112 mg/mL

Dissociation Constants: $pK_a = 2.65$

Partition Coefficient$_{(n\text{-octanol/water})}$: $\log K_{ow} = -0.693$ (pH 4), -0.670 (pH 7), -0.693 (pH 10)

The partition coefficient (*n*-octanol/water) was determined using the flask-shaking method following OECD Guideline 107 and according to Good Laboratory Practices (GLP) (AD-162-2002).

Adsorption Coefficient: K_d (activated sludge) = 5.97 – 12.9
K_{oc} (organic carbon) = 21.1 – 45.6

The adsorption coefficient for FTC was determined following the OECD Guideline 106 and according to GLP (AD-162-2001). It was concluded that FTC does not significantly absorb to activated sludge.

Vapor Pressure: Assumed to be nonvolatile

4.1.3. Environmental Depletion Mechanisms

Ultraviolet-Visible Absorption Spectrum: Absorbs in the UV range, assumed not to be photolabile

Hydrolysis: No data available

Aerobic Biodegradation in Water: Not considered readily biodegradable

FTC was tested to assess its degree of ready biodegradability using the procedure outlined in the OECD guideline 301D and according to GLP for the "Ready Biodegradability Closed Bottle Test" (Report 1784). The results indicate that FTC is not readily biodegradable under the conditions tested.

Aerobic and Anaerobic Transformation in Aquatic Sediment Systems: >10% AR associated with sediment from Day 2; System DT_{50} 36-151 days; No significant metabolites formed.

A GLP study was conducted to assess the degradation of [^{14}C]-FTC in natural water-sediment systems. The rate of aerobic and anaerobic transformation of parent [^{14}C]-FTC was studied at a concentration of 1.0 mg/L in darkness at 20 ± 2ºC for 100 days in two aerobic and anaerobic sediments varying in pH, textual characteristics, organic matter content and microbial content. The study was conducted according to OECD Guideline 308 and according to GLP (AD-162-2004).

Under aerobic water/sediment conditions, FTC degraded at a moderate rate. FTC decreased from an average of 102.9 and 106.7% applied radioactivity (AR) on day 0 to 66.0 and 14.5% AR at study termination (day 100) for the aerobic sandy loam and sand sediments, respectively. 11.7% and 54.3% of applied radioactivity was converted to $^{14}CO_2$ in the sandy loam aerobic and sandy aerobic sediments, respectively.

The whole system disappearance time for a 50% reduction (DT_{50}) and 90% reduction (DT_{90}) was calculated using single first-order (SFO) kinetics, as summarized in below. The primary FTC degradation product was CO_2 and no significant metabolites were formed.

Table 1. Aerobic Total System Degradation Kinetics

System	Compartment	Model	K (days^{-1})	DT_{50} (days)	DT_{90} (days)
Taunton River (Sandy Loam Sediment)	Total System	SFO	-0.0046	150.7	500.7
Weweantic River (Sandy Sediment)	Total System	SFO	-0.0193	35.91	119.3

4.1.4. Environmental Concentrations

The metabolism of FTC will result in excreted drug substance being introduced into the environment primarily through municipal sewage treatment plants (STPs) or septic tanks.

Environmental Introduction Concentration (EIC): The EIC entering the aquatic environment from patient use is calculated without including consideration of metabolism or environmental depletion mechanisms that occur in the waste treatment process. The EIC from patient use is based on the highest annual quantity of the active moiety expected to be produced for use during the next five years; the quantity used in all dosage forms and strengths included in this application; and the quantity used in related applications for FTC.

The calculation of the EIC for the aquatic environment assumes all drug products produced in a year are used and enter the publicly owned treatment works (POTWs), even distribution throughout the US per day, and no metabolism or depletion mechanisms. The EIC was calculated using the following formula from the FDA Guidance Document as follows:

EIC-Aquatic (ppb) = A × B × C × D

where

A = It is expected that FTC will not exceed 50,000 kg/year
B = $1/1.214 \times 10^{11}$ liters/day per day entering publicly owned treatment works (POTWs)
C = year/365 days
D = 10^9 µg/kg (conversion factor)

Using this calculation, the EIC from patient use of FTC is approximately 1.13 ppb.

Because FTC is not readily biodegradable (to CO_2), a conservative/protective assumption of this environmental risk assessment is that the EIC, Expected Environmental Concentration (EEC) and Maximum Expected Environmental Concentration (MEEC) for FTC are similar.

In summary, based on the estimated production data, the MEEC is 1.13 µg/L (1.13 ppb) which requires a (full) Environmental Assessment and not a Request for Categorical Exclusion (RCE) from a full Environmental Assessment under the FDA Guidance Document.

4.1.5. Summary of Environmental Fate of the Substance

The data available suggests that the majority of dosed FTC will be excreted by patients and hence the total dose is representative of the loading to STPs.

Once in municipal STPs, the available data suggests FTC will not be rapidly degraded and is unlikely to bind to sewage solids, which are removed after settling. The adsorption coefficient is sufficiently low to suggest that FTC will not reach the terrestrial soil environment, through the route of spreading of sewage sludge on agricultural land.

Once emitted to surface water, FTC appears to partition to sediment over time. If present in sediment, FTC has variable rates of biodegradation, seeming to be somewhat recalcitrant in sandy loam sediment but fairly well mineralized in sand sediment. Formation of non-extractable residues and mineralization appears to be the major route of removal from sediment/water systems.

The estimated log K_{ow} values indicate that FTC is not lipophilic across the pH range of 4 – 10, which is considered to the pH range which encompasses most environmental situations, as such potential for bioconcentration is low.

As the MEEC exceeded 1 ppb, as per the FDA Guidance Document, an evaluation of the environmental effects of FTC was performed including an assessment of risk based on the MEEC and comparison to Assessment Factors as per the FDA Guidance Document. Based on the fate and effects testing, the environmental impact focused on sewage treatment microbes, acute and chronic aquatic species, and sediment species.

4.2. Environmental Effects of Released Substances

A tiered approach to environmental effects testing of FTC as per the FDA Guidance Document, including a risk assessment evaluation compared to Assessment Factors. As FTC partitions to water based on the above data, effects of released substances on aquatic organisms was conducted for potential acute and chronic effects.

4.2.1. Acute Toxicity (Tier 1 and 2)

4.2.1.1. Sewage Microorganisms

A GLP respiratory inhibition study was conducted with FTC (Lot No. PP-0053-5044, purity of 99.8%) according to OECD Guideline 209, “Activated Sludge, Respiration Inhibition Test” (1993) to determine the concentration which would potentially inhibit the respiratory activity of sewage treatment plant (STP) activated sludge microorganisms (AD-162-2003).

Methods

FTC was tested at concentrations of 0.1, 1.0, 10, 100 and 1000 $mg.L^{-1}$ and 3,5-dichlorophenol was also assayed as a positive control to ensure test validity. Duplicate control vessels were also included in the test.

Prepared vessels were aerated for 3 h, after which dissolved oxygen concentrations were measured for an 8 - 10 min period. The respiration rate ($mg\ O_2.L^{-1}.h^{-1}$) was calculated over the linear phase of oxygen consumption for each vessel. The respiration inhibition (%) for FTC test solutions was calculated by comparison of respiration rate with the control.

Findings

Oxygen consumption in the test vessels at 0.1, 1.0, 10, 100 and 1000 $mg.L^{-1}$ of FTC was 14.6, 14.5, 15.0, 15.7 and 15.3 $mg\ O_2.L^{-1}.hr^{-1}$, respectively, compared with mean control values of 15 $mg\ O_2.L^{-1}.hr^{-1}$. Respiratory inhibition for FTC was 2.5, 3.0, 0.0, 0.0 and 0.0% at the increasing concentrations tested, respectively. The no observed effect concentration (NOEC) for FTC was ≥ 1000 $mg.L^{-1}$ and the median effective concentration (EC_{50}) was estimated to be > 1000 $mg.L^{-1}$.

4.2.1.2. Green Freshwater Algae (*Pseudokirchneriella subcapitata*) Test

The toxicity of FTC (Lot No. PP-0053-5044, purity of 99.8%) to green freshwater algae was investigated, following OECD Guideline 201, "Algae, Growth Inhibition Test" (2006) and according to GLPs (TX-162-2002).

Methods

Based on the results of a range finding test, a definitive test was conducted with solutions prepared at the following nominal concentrations 0.32, 1.0, 3.2, 10, 32 and 100 $mg.L^{-1}$ (three replicates each) tested together with an untreated control (six replicates).

The test solutions were prepared in algal growth media by serial dilution of a 100 $mg.L^{-1}$ stock solution. 100 mL aliquots of the prepared test solutions were transferred to test vessels and 0.88 mL of exponentially growing *Pseudokirchneriella subcapitata* culture was inoculated into each flask. The test vessels were incubated on an orbital incubator (100 rpm) within an environmental chamber under continuously illuminated (4,440 to 5,900 lux; 21 to 25 °C) for 72 h. Samples were taken from each test vessel every 24 h for determination of cell concentration using a hemocytometer.

The NOEC and the concentration that resulted in a 10, 20 and 50% reduction in growth rate (E_rC_{10}, E_rC_{20} and E_rC_{50}, respectively) and yield (E_yC_{10}, E_yC_{20} and E_yC_{50}, respectively) were estimated.

Findings

Chemical analysis of test samples taken at 0 and 72 h indicated that FTC was stable over the test period, remaining within ± 20% of nominal concentrations. The mean measured concentrations were 0.34, 1.2, 3.7, 11, 33 and 110 $mg.L^{-1}$ for the 0.32, 1.0, 3.2, 10, 32 and 100 $mg.L^{-1}$ nominal concentrations, respectively.

Daily cell concentrations were used to calculate inhibition compared to the control of average specific growth rates and yield. Statistical analysis using William's test revealed no significant reduction in growth rate or yield in any treatment group compared to the control. Therefore the 72 hour NOEC for growth rate and yield was determined as ≥110 $mg.L^{-1}$. The 0 - 72 hour E_rC_{10}, E_rC_{20}, E_rC_{50} and E_yC_{10}, E_yC_{20}, E_yC_{50} values were estimated to be >110 $mg.L^{-1}$, the highest concentration tested.

4.2.1.3. Invertebrate – Water Flea (*Daphnia magna*)

The toxicity of FTC (Lot No. PP-0053-5044, purity of 99.8%) to the water flea (*Daphnia magna*) was investigated, following OECD Guideline 202, "Daphnia sp., Acute Immobilization Test" (2004) and according to US GLPs (TX-162-2003).

Methods

Daphnia magna were exposed to nominal test concentrations of 6.3, 13, 25, 50 and 100 $mg.L^{-1}$. Daphnids were selected impartially from the culture vessels and placed in each test beaker by adding no more than two daphnids to each beaker until all beakers contained two daphnids. This procedure was repeated until each beaker contained five daphnids. The number of immobilized daphnids in each replicate test vessel was recorded at 24 and 48 hours of exposure. Immobilization was defined as those animals not able to swim within 15 seconds after gentle agitation of the test vessel. Biological observations and observations of the physical characteristics of each replicate test solution were also made and recorded at 0, 24 and 48 hours. The mean measured concentrations tested and the corresponding immobilization data derived from the definitive toxicity test were used to estimate the 24- and 48-hour median effective and no-effect concentrations (EC_{50} and NOEC).

Findings

The mean measured concentrations were 7.2, 14, 29, 54 and 110 $mg.L^{-1}$. Following 48 hours of exposure, no immobilization or adverse effects were observed among daphnids exposed to any treatment level tested (up to a concentration of 110 $mg.L^{-1}$) or the control. The 48-hour EC_{50} value for FTC in Daphnia magna was empirically estimated to be >110 $mg.L^{-1}$, the highest mean measured concentration tested. The NOEC, the highest concentration producing 0% immobilization, was determined to be 110 $mg.L^{-1}$.

4.2.1.4. Fish Acute Toxicity

The effects of FTC (Lot No. PP-0053-5044, purity of 99.8%) on the acute toxicity of fish was investigated with Rainbow Trout (*Oncorhynchus mykiss*), according to OECD Guideline 203, “Fish, Acute Toxicity Test” (1992) and US GLPs (TX-162-2004).

Methods

Rainbow trout were exposed, under static conditions, to nominal FTC concentrations of 6.3, 13, 25, 50 and 100 $mg.L^{-1}$, respectively for 96 hours. The test was initiated when rainbow trout (10 fish per treatment level and the control) were impartially selected and distributed to each aquarium. All aquaria were examined at 0, 24, 48, 72 and 96 hours of exposure as follows: mortalities were recorded and removed, biological observations, including adverse effects (e.g., darkened pigmentation), of the exposed rainbow trout and observations of the physical characteristics of the test solutions (e.g., presence of precipitate, film on the solution's surface) were made and recorded. Effects for this study were based on death, defined as the lack of movement by the exposed organisms (i.e., absence of gill movement and reaction to gentle prodding). The mean measured concentrations tested and the corresponding mortality data derived from the definitive toxicity test were used to estimate the 24-, 48-, 72- and 96-hour median lethal concentrations (LC_{50}) and the NOEC.

Findings

The mean measured concentrations were 7.0, 13, 25, 51 and 110 $mg.L^{-1}$. Following 96 hours of exposure, no adverse effects or mortality were observed among rainbow trout exposed to any treatment level tested (up to a concentration of 110 mg/L^{-1}) or the control. The 96-hour LC_{50} value for FTC on Rainbow Trout was empirically estimated to be >110 $mg.L^{-1}$, the highest mean measured concentration tested. The NOEC was determined to be 110 $mg.L^{-1}$.

4.2.1.5. Acute Aquatic Ecotoxicity Testing and Assessment

FTC was evaluated in acute studies in sewage microorganisms, algae, daphnia, fish, and sewage microorganisms (OECD 209, 201, 202 and 203 respectively). All studies were conducted in accordance with GLP. Data are summarized in the table below.

Table 2. Acute Toxicity Studies in Aquatic Organisms

Study	Result	EC_{50} or LC_{50} / MEEC[1]	Reference
Activated Sludge, Respiration Inhibition Test (OECD 209)	NOEC ≥ 1000 $mg.L^{-1}$ EC_{50} > 1000 $mg.L^{-1}$	885,000	AD-162-2003
Tier 1 - Freshwater Green Algae (OECD 201) *Pseudokirchneriella subcapitata*	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$	97,000	TX-162-2002
Water Fleas (OECD 202) *Daphnia magna*	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$	97,000	TX-162-2003
Rainbow Trout (OECD 203) *Oncorhynchus mykiss*	NOEC ≥ 110 $mg.L^{-1}$ LC_{50} > 110 $mg.L^{-1}$	97,000	TX-162-2004

1 All values approximated to the nearest thousand

The calculated assessment factors in all cases are greater than the required factors (1,000x for Tier 1 and 100x for Tier 2) and in no case were sub-lethal effects observed at concentrations equal to the MEEC. The margin calculations did not factor in the 10-fold dilution typically observed from the POTW to the aquatic system which would increase the margins 10x for algae, water fleas, and fish. These results indicate that FTC release to sewage treatment plants and subsequently to the environment does not pose an environmental risk.

Based on the data above, there is no need to perform Tier 3 Chronic Toxicity testing. However, data was available and thus reported in Section 4.2.2.

4.2.2. Chronic Toxicity (Tier 3)

4.2.2.1. Fish Early Life Stage Test

The effects of FTC (Lot No. PP-0053-5044, purity of 99.8%) on the early life stages of fish was investigated with fathead minnows (*Pimephales promelas)*, according to OECD Guideline 210, “Fish, Early-Life Stage Toxicity Test” (1992) and GLP (TX-162-2005).

Methods

Fathead minnow embryos and fry were exposed, in a flow-through system, for 28 days post-hatch to nominal FTC concentrations of 0.63, 1.3, 2.5, 5.0 and 10 $mg.L^{-1}$, respectively. The experiment (nominal day 0) started with 120 fresh and healthy fertilized fathead minnow eggs per test group, with each test group consisting of two replicate exposure vessels. The fertilized eggs were randomly distributed between twelve egg incubation cups. Each incubation cup contained 60 eggs was suspended in individual exposure aquaria. Test solutions were constantly renewed at a rate of approximately 6.7 aquarium volumes per 24 hours.

Findings

Chemical analysis of test samples taken at Days 0, 1, 5, 12, 19, 26 and 33 indicated that mean measured concentrations of FTC were 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ (between 110-130 % of nominal).

At the completion of hatch (day 5), hatching success in the control averaged 77%. Embryo hatching success in the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels was 80, 78, 70, 78 and 78%, respectively. Kruskal-Wallis' Test determined no significant difference in embryo hatching success among organisms exposed to any treatment level tested as compared to the embryo hatching success of the control organisms. No deformed fry were observed in any treatment level tested or the control.

Following 28 days post-hatch exposure, larval survival in the control averaged 98%. Larval survival in the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels was 95, 98, 95, 98 and 95%, respectively. Williams’ Test determined no significant difference in larval survival in any treatment level tested as compared to the control.

At test termination, total length of larvae exposed to the control averaged 28.6 mm. The mean total length of larvae exposed to the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels was 28.4, 28.2, 28.7, 27.9 and 28.2 mm, respectively. Statistical analysis (Williams' Test) demonstrated no statistically significant reductions in larval length among larvae exposed to any treatment level tested as compared to the control.

Dry weight of larvae in the control averaged 0.0516 g. Dry weight of larvae exposed to the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels averaged 0.0505, 0.0486, 0.0526, 0.0484 and 0.0471 g, respectively. Statistical analysis (Williams’ Test) demonstrated a statistically significant reduction in dry weight among larvae exposed to the 11 $mg.L^{-1}$ treatment level compared to the control.

Based on the overall results of this study, the Lowest-Observed- Effect Concentration (LOEC) in the early life-cycle of fathead minnows was determined to be 11 $mg.L^{-1}$, the highest mean measured concentration tested. The NOEC was determined to be 6.1 $mg.L^{-1}$.

4.2.2.2. Aquatic Invertebrate (*Daphnia magna*) Reproduction Test

The effects of FTC (Lot No. PP-0053-5044, purity of 99.8%) on the reproduction of the aquatic cladoceran *Daphnia magna* were investigated, according to OECD Guideline 211, "Daphnia magna Reproduction Test" (1998) and GLP (TX-162-2006).

Methods

Based on the results of a range-finding test, the definitive test was conducted with the following nominal FTC concentrations, 6.3, 13, 25, 50 and 100 $mg.L^{-1}$. The definitive test was performed using a semi-static design with 10 vessels per test concentration and the untreated control group. Each of the vessels contained one neonate (< 24 h old) *Daphnia magna* in 80 mL test medium.

The test duration was 21 days and the test solutions were renewed 2 - 3 times per week. Test solutions were prepared by serial dilution of a 100 $mg.L^{-1}$ stock solution. The daphnids were fed on a daily basis with a green alga (*Anistrodesmus falcatus*) suspension and a suspension of yeast, cereal leaves and digested flake fish food. During the test, samples of newly prepared test solutions on days 0, 2, 16 and 19 were collected from each treatment group and the control for analytical confirmation of FTC concentration. Additionally, samples of the aged test solutions were collected for analyses on days 2, 5, 19 and 21.

The condition of the parental daphnids and the number offspring produced was monitored daily. The body length of the parental daphnids was measured at the end of the test. Dissolved oxygen, temperature and pH were measured in each test and control solution at the beginning (fresh solutions) and end (aged solutions) of each renewal period.

Findings

Mean measured concentrations of FTC were 7.1, 14, 28, 56 and 110 $mg.L^{-1}$ (110 – 130 % nominal). The FTC concentrations were suitably maintained during the renewal period, the recovery in the aged solutions ranged from 110 – 130% of nominal. The effect parameters were based on the mean measured exposure concentrations.

The first offspring were observed on day 8 at all test concentrations, including the control. The number of immobile adult *D. magna* recorded during the study were 1 (10%) in the control, 28 and 56 $mg.L^{-1}$ test groups, 2 (20%) in the 110 $mg.L^{-1}$ test group and 0 (0)% in the 7.1 and 14 $mg.L^{-1}$ test groups. At the highest FTC dose (110 $mg.L^{-1}$) the mean number of offspring produced per surviving *D. magna* was 155, a reduction of approximately 12% compared to the control. Statistical analysis, using Bonferroni's Test, determined this reduction to be non-significant and therefore the NOEC for reproduction was determined to be $\geq$ 110 $mg.L^{-1}$.

No statistically significant difference (Fisher exact) was detected between the parental survival or mean body length, of any treatment group compared to the control. The 21 day FTC NOEC for each endpoint observed during this study was determined to be $\geq$110 $mg.L^{-1}$.

4.2.2.3. Effects on Larvae of the Midge *Chironomus riparius*

The effects of FTC ([^{14}C]-FTC; batch 645-101-0582, radiochemical purity of 99.6%. FTC; Lot No. 2983-AC-104, purity 99.8%) on the pre-emergent aquatic early life stages of the insect *Chironomus riparius* were investigated, according to OECD Guideline 218, "Sediment Water Chironomid Toxicity Test Using Spiked Sediment" (2004) and GLP (TX-162-2007).

Methods

Following an initial range finding test, a definitive test was conducted with a nominal sediment dry weight concentrations of 1.2, 3.6, 11, 33 and 100 mg.kg^{-1}.

The study was conducted by spiking conditioned artificial sediment (following OECD 218; 1.9% organic carbon, pH 6.6) with appropriate volumes of [^{14}C]-FTC in solvent, so as to give the required nominal concentrations. After ensuring homogeneity, a 1.5 cm layer (123 g wet weight) of the prepared sediments were placed in 600 mL capacity vessels and a 6 cm layer (300 mL) of freshwater carefully delivered over the sediment so as to avoid disturbance of the sediment. The ratio of sediment to water was approximately 1:4 and the total volume of the test system was approximately 375 mL. Four replicate exposure vessels were prepared for each treatment level and controls (untreated and solvent) to monitor the biological results (i.e., percent emergence and development rate) of the exposed midges. Three additional replicate vessels were also prepared for each treatment level and solvent control for analytical measurements to determine exposure concentrations of FTC in the overlying water, pore water and sediment.

After a 2 day equilibration period, ~20 first-instar midge larvae were added to each of the in-life vessels. Midge larvae were provided with food daily and adult emergence recorded up to 28 days post initiation. The endpoints of the test were emergence (%), development time and development rate (1.d^{-1}).

Findings

Results of the sediment sample analysis showed that measured concentrations at preparation were close to nominal (105 -118%). However, concentrations in the aqueous test system were lower, 38 – 67% of nominal on Day 0 and 9.4 – 15% of nominal by test termination on Day 28. The drop in sediment was not reciprocated with concurrent increases in either pore or overlying water concentrations, as such mineralization to $^{14}CO_2$ is the most likely explanation for the lost activity in each test system. The test system will have an initial concentration of active microbes, whose population will have been greatly enhanced by the daily feeding regime with fish food, which may explain the extensive degradation seen.

The first midge emergence in the control was observed on Day 13. Following 28 days of exposure, percent emergence and mean development in the control was 95% and 0.0655, respectively. These results are within the minimum standard criteria established in the OECD guideline, i.e. ≥ 70% emergence and emergence between days 12 and 23. Midge emergence from all the test concentrations was comparable to the controls and statistical analysis, using Dunnett's test determined no significant difference between any treatment level and the controls.

No significant (Dunnett's test) difference in development rate between test groups and the controls was observed. No biological significant effect on emergence rate and development rate was found at the initial measured concentration of 38 $mg.kg^{-1}$, the highest concentration tested. Therefore, the overall NOEC of FTC to *Chironomus riparius* was determined as ≥ 38 $mg.L^{-1}$. Since there was ≤ 50% inhibition of emergence or development rate, the 28-day EC_{50} was estimated to be > 38 $mg.kg^{-1}$ dry weight, based on the initial measured concentration.

Normalized NOEC

As per EMA guidelines {European Medicines Agency (EMEA) 2016} the results from the results from the sediment toxicity tests were recalculated into standard sediment with an organic carbon content of 10%.

$$NOEC_{standard\ sediment} = NOEC_{measured} \times \frac{foc_{standard\ sediment}}{foc_{measured}}$$

Symbol	Parameter	Value (Reference)
Input		
$NOEC_{measured}$	Sediment dweller test NOEC	38 mg kg_{dwt}^{-1}
$foc_{standard\ sediment}$	Fraction of organic carbon standard sediment	0.1 (10%) {European Medicines Agency (EMEA) 2016}
$foc_{measured}$	Fraction of organic carbon test sediment	0.019 (1.9%) (Section 4.2.2.3)
Output		
$NOEC_{standard\ sediment}$	Standard sediment normalized NOEC	200 $mg.kg_{dwt}^{-1}$

4.2.2.4. Tier 3 Assessment

Although not obligated to be performed under the FDA Guidance Document and as part of Gilead's product stewardship efforts, Tier 3 ecotoxicity testing including chronic studies in fish (fathead minnow), water flea, and sediment dweller midge studies were performed.

The concentration in freshly deposited sediment is taken as the PEC for sediment; therefore, the properties of suspended matter are used. The concentration in bulk sediment can be derived from the corresponding water body concentration, assuming a thermodynamic partitioning. The $MEEC_{sediment}$ was calculated following the methodology provided in {European Chemicals Agency 2016, European Medicines Agency (EMEA) 2016} as follows:

$$MEEC_{\text{sediment}} = \frac{K_{susp-water}}{RHO_{susp}} \times MEEC \times CONV_{susp} \times 1000$$

$$K_{susp\text{-}water} = Fwater_{susp} + Fsolid_{susp} \times Kp_{susp} / 1000 \times RHO_{solid}$$

$$CONV_{susp} = \frac{RHO_{susp}}{Fsolid_{susp} \times RHO_{solid}}$$

$$Kp_{susp} = Foc_{susp} \times Koc$$

Symbol	Parameter	Value (Reference)
Input		
MEEC	Maximum expected environmental Concentration (in the water)	1.13 µg.L^{-1} (Section 4.1.4)
$Fwater_{susp}$	Fraction water in suspended matter	0.9 m^3.m^{-3} {European Chemicals Agency 2016}
$Fsolid_{susp}$	Fraction solids in suspended matter	0.1 m^3.m^{-3} {European Chemicals Agency 2016}
RHO_{solid}	Bulk density of solids	2500 kg m^{-3} {European Chemicals Agency 2016}
Foc_{susp}	Weight fraction organic carbon in suspended matter	0.1 kg kg^{-1} {European Chemicals Agency 2016}
K_{oc}	Organic carbon normalised partition coefficient	45.6 dm^3 kg^{-1} (worst-case see Section 4.1.2)
RHO_{susp}	Bulk density of suspended matter	1150 kg m^{-3} {European Chemicals Agency 2016}
1000	Conversion factor	1000 dm^3.m^{-3} {European Chemicals Agency 2016}
Intermediate Results		
$K_{susp\text{-}water}$	Sediment matter water partition coefficient (v/v)	2.04 m^3 m^{-3}
Kp_{susp}	Partition coefficient solids and water in suspended matter (v/w)	4.56 L.kg^{-1}
$CONV_{susp}$	Conversion factor for sediment concentrations: wwt to dwt	4.6 kg$_{wwt}$.kg$_{dwt}$$^{-1}$
Output		
$MEEC_{sediment}$	Predicted Environmental Concentration in sediment	9.2 µg kg$_{dwt}$$^{-1}$ 2.0 µg.kg$_{wwt}$$^{-1}$

All studies were conducted in accordance with GLPs. Data are summarized in the Table 3. Based on these data, (though not obligated to be performed under the FDA Guidance Document), a Tier 3 Assessment was performed. The Test Tier 3 Assessment compares the lowest EC_{50} or LOEC of chronic or reproductive studies to the MEEC. As per the FDA Guidance Document, if the ratio is ≥ 10 and there are no effects at the MEEC, no environmental impact is anticipated. Since the NOEC ranged from 5,000 – 97,000 greater than the MEEC for three different organisms, no environmental impact is anticipated. The margin calculations did not factor in the 10-fold dilution typically observed from the POTW to the aquatic system which would increase the margins 10-fold.

Table 3. Tier 3 Chronic and Reproductive Toxicity Studies

Study	Results	NOEC / MEEC[1]	Reference
Fathead Minnow (OECD 210) *Pimephales promelas* Fish Early Life Cycle	LOEC = 11 $mg.L^{-1}$ NOEC = 6.1 $mg.L^{-1}$	5,000	TX-162-2005
Water Fleas (OECD 211) *Daphnia magna* Reproduction	NOEC ≥ 110 $mg.L^{-1}$ LOEC > 110 $mg.L^{-1}$	97,000	TX-162-2006
Sediment Dwellers (OECD 218) Chironomid Larvae Toxicity	NOEC ≥ 200 $mg.kg_{dwt}^{-1}$ LOEC > 200 mg kg_{dwt}^{-1}	22,000	TX-162-2007

1. All values approximated to the nearest thousand. $MEEC_{sediment}$ values used for the Chironomid (OECD 218) study

4.3. Summary

A standard battery of environmental fate and effects studies has been conducted to evaluate the environmental risk associated with the use of FTC. FTC is likely to partition mostly into water and sediment and not bioaccumulate in the environment.

A battery of acute, chronic and reproductive effects studies were conducted in aquatic organisms and sediment dwellers. The results of these studies showed low toxicity. The results of these studies were compared to the MEEC. The EC_{50} and LC_{50} concentration / MEEC ratios at all three tiers of assessment based on one (1) acute study (Tier 1), a battery of acute studies (Tier 2), and chronic studies (Tier 3) were greater than their required assessment factors (1000x for Tier 1, 100x for Tier 2, and 10x for Tier 3) and there were no effects observed at the corresponding MEEC. Based on the above data and risk assessment conclusions, the current data indicates that FTC is of low risk to the environment based on current use patterns. Gilead therefore requests approval for the anticipated use based on no environmental impact of this clinical use.

5. MITIGATION MEASURES

Based on the evidence presented, no environmental mitigation measures are needed.

6. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action and therefore no alternatives are proposed.

7. LIST OF PREPARERS

Joel Bercu, PhD MPH DABT

Education

Indiana University School of Informatics Indianapolis, IN	PhD	Health Informatics (Focus in Toxicology)	2010
University of Texas School of Public Heath Houston, TX	MPH	Toxicology	2001
Texas A&M University College Station, TX	BS	Biomedical Sciences	1998

Job History

Gilead Sciences Drug Safety Evaluation 333 Lakeside Drive Foster City, Ca 94404	Director	2015-present

- Lead of the Environmental and Occupational Toxicology group
- Manage Environmental Risk Assessments (ERAs) for Gilead compounds, including the environmental toxicity and fate studies
- Oversee derivation of Occupational Exposure Limits (OELs) for worker safety
- Oversee derivation of Permissible Daily Exposures (PDEs) for pharmaceutical cleaning validation
- Oversee GHS classification and Safety Data Sheet language development
- Manage the assessment of impurities, including QSAR assessment of mutagenic impurities, PDEs for reagents, solvents and metals, extractables and leachables, and qualification toxicity testing
- Manage occupational health hazard testing of Gilead compounds

Amgen Product Stewardship One Amgen Center Drive Thousand Oaks, Ca	EHS Sr. Manager	2010-2015

- Lead of the Product Stewardship group which provided toxicology assessments for product and occupational safety, hazard information on Safety Data Sheets, ERAs, and risk assessments for non-conformance investigations
- Chair of the Hazard Evaluation Committee which decides safe exposure levels to pharmaceuticals (occupational and product safety), and hazardous chemicals
- Global industry leader in risk assessment for emerging issues and regulatory guidance documents

Lilly Research Laboratories	Consultant Toxicologist	2008-2010
Eli Lilly and Company	Assistant Sr. Toxicologist	2004-2008
Indianapolis, IN	Toxicologist	2000-2004
Risk Assessment Group		

- Risk assessment leader for chemistry and quality to ensure the manufacture of pharmaceuticals are safe from potential residual levels of hazardous chemicals such as mutagens, carcinogens, or reproductive toxicants

Lyondell Chemical Company Houston, TX	Toxicologist	1999-2001
University of Texas Houston School of Public Health Houston, TX	Graduate Research Assistant	1998-2001
Moffitt Cancer Center	Research Assistant	1997

Certifications / Expertise

Diplomat of the American Board of Toxicology
Environmental and Occupational Toxicology
Benchmark Dose Modeling
Computer Modeling / Informatics
Threshold of Toxicological Concern
Toastmasters – Competent Communicator

Professional Associations

Society of Toxicology 1999 – present

- Occupational Health Specialty Section (Served as President and Vice President)
- Risk Assessment Specialty Section

PhRMA LDKIT (Chair of Risk Assessment Subgroup) 2010 – 2015

- Led the development of ICH M7 (i.e., mutagenic impurities) and its corresponding addendum

ILSI HESI Workgroups 2009 – 2011

- Short-Term / Intermittent Exposure to Carcinogens
- Risk Assessment of Multiple Carcinogens
- Threshold of Toxicological Concern

Publications

Bercu JP, Morinello E, Sehner C, Shipp BK, Weideman PA. 2016. Point of departure (PoD) selection for the derivation of Acceptable Daily Exposures (ADEs) for active pharmaceutical ingredients (APIs). Regul Toxicol Pharmacol. 2016. doi: 79 Suppl 1:S48-56.

Hayes EP, Jolly RA, Faria E, Barle EL, Bercu J, Molnar L, Naumann B, Olson M, Pecquet A, Sandhu R, Shipp BK, Sussman R, Weideman P. 2016. A harmonization effort for acceptable daily exposure application to pharmaceutical manufacturing - Operational considerations. Regul Toxicol Pharmacol. 79 Suppl 1:S39-47.

Faria EC, Bercu JP, Dolan DG, Morinello EJ, Pecquet AM, Seaman C, Sehner C, Weideman PA. 2016. Using default methodologies to derive an acceptable daily exposure (ADE). Regul Toxicol Pharmacol. 2016. 79 Suppl 1:S28-38.

Amberg A, Beilke L, Bercu J, Bower D, Brigo A, Cross KP, Custer L, Dobo K, Dowdy E, Ford KA, Glowienke S, van Gompel J, Harvey J, Hasselgren C, Honma M, Jolly R, Kemper R, Kenyon M, Kruhlak N, Leavitt P, Miller S, Muster W, Nicolette J, Plaper A, Powley M, Quigley DP, Reddy MV, Spirkl HP, Stavitskaya L, Teasdale A, Weiner S, Welch DS, White A, Wichard J, Myatt GJ. 2016. Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses. Regul Toxicol Pharmacol. 77:13-24.

Weideman, P, Bercu JP, Callis C, Dolan DG, Faria E, Flueckiger A, Gould J. Hayes EP, Jolly R, Barle EL, Luo W, Molnar LR, Morinello E, Naumann BD, Olson M, Pfister T, Sandhu R, Sargent, EV, Seaman C. 2015. Deriving health-based exposure limits in the pharmaceutical industry. Contract Pharma. 17(7):74.

Stanard B, Dolan DG, Hanneman W, Legare M, Bercu JP. 2015. Threshold of toxicological concern (TTC) for developmental and reproductive toxicity of anticancer compounds. Regul Toxicol Pharmacol. 72(3):602-9.

Pfister T, Dolan D, Bercu J, Gould J, Wang B, Bechter R, Barle EL, Pfannkuch F, Flueckiger A. 2014. Bioavailability of Therapeutic Proteins by Inhalation—Worker Safety Aspects. Ann. Occup. Hyg. 58(7):899-911.

Galloway SM, M. Reddy MV, McGettigan K, Gealy R, Bercu JP. 2013. Potentially mutagenic impurities: Analysis of structural classes and carcinogenic potencies of chemical intermediates in pharmaceutical syntheses supports alternative methods to the default TTC for calculating safe levels of impurities. Regul. Toxicol. Pharmacol. 66(3):326-35.

Bercu JP, Sharnez R, Dolan DG. 2013. Advancing Toxicology in RiskMAPP: Setting ADEs Based on the Subsequent Drug Substance. Regul. Toxicol. Pharmacol. 65(1):157-61.

Bercu JP, Dolan DG. 2013. Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials. Regul. Toxicol. Pharmacol. 65(1):162-7.

Sharnez R, Aisenbrey E, Bercu J, Binkley D, Tholudur A. 2012. Cleaning validation of multiproduct equipment— Acceptance limits for inactivated product. Part II—Application of the comparable quality approach to intrasite assessments. J. Validation Technol. 18(2):17-25.

Felter SP, Conolly RB, Bercu JP, Bolger PM, Boobis AR, Bos PMJ, Carthew P, Doerrer NG, Goodman JI, Harrouk WA, Kirkland DJ, Lau SS, Llewellyn GC, Preston RJ, Schoeny R, Schnatter AR, Tritscher A, van Velsen F, Williams GM. 2011. A Proposed Framework for Assessing Risk from Less-Than-Lifetime Exposures to Carcinogens. Crit. Rev. Toxicol. 41(6):507-44.

Bercu JP, Jolly RA, Flagella KM, Baker TK, Romero P, Stevens JL. 2010. Toxicogenomics and cancer risk assessment: A framework for key event analysis and dose-response assessment for nongenotoxic carcinogens. Regul. Toxicol. Pharmacol 58(3):369-81.

Bercu JP, Morton SM, Deahl JT, Gombar VK, Callis CM, van Lier RBL. 2010. *In silico* approaches to predicting cancer potency for risk assessment of genotoxic impurities in drug substances. Regul. Toxicol. Pharmacol. 57(2-3):300-6.

Raillard SP, Bercu JP, Riley CM, Baertschi SW. 2010. Prediction of drug degradation pathways leading to potential genotoxic impurities. Org. Proc. Res. Dev. 14(4): 1015-1020.

Baertschi SW, De Antonis D, McKeown A, Bercu JP, Raillard S, Riley CM. 2010. Stress testing as a predictive tool for the assessment of potential genotoxic degradants. In: Pharmaceutical Stress Testing: Predicting Drug Degradation, 2nd Ed. (Editors: S.W. Baertschi SW, Alsante KM, and Reed RA). Informa Life Sciences.

Callis CM, Bercu JP, DeVries KM, Dow LK, Robbins DK, Varie DL. 2010. Risk assessment of genotoxic impurities in marketed compounds administered over a short-term duration: Applications to oncology products and implications for impurity control limits. Org. Proc. Res. Dev. 14(4): 986-992.

Bercu JP, Dobo KL, Gocke E, McGovern T. 2009. Summary of Symposium: Overview of genotoxic impurities in pharmaceutical development. Int. J. Toxicol. 28(6): 468-78.

Bercu JP, Callis CM. 2009. Comprehensive toxicology risk assessment for genotoxic impurities. Org. Proc. Res. Dev. 13(5): 938.

Dobo KL, Obach RS, Luffer-Atlas D, Bercu JP. 2009. A strategy for risk assessment for human genotoxic metabolites. Chem. Res. Toxicol. 22(2): 348-56.

Bercu JP, Hoffman WP, Lee C, Ness DK. 2008. Quantitative assessment of cumulative carcinogenic risk for multiple genotoxic impurities in a new drug substance. Regul. Toxicol. Pharmacol. 51(3): 270-7.

Bercu JP, Parke NJ, Fiori JM, Meyerhoff RD. 2008. Human health risk assessments for three neuropharmaceutical compounds in surface waters. Regul. Toxicol. Pharmacol. 50(3): 420-7.

Bercu JP. 2001. Compounds that bind to the gamma-aminobutyric acid benzodiazepine ionophore complex modulate the cellular response to oxidant stress. University of Texas Health Science Center at Houston. School of Public Health.

Abstracts/Invited Presentations

Bercu JP. 2016. Incorporating (Q)SAR and Expert Reviews to Ensure Compliance with ICH M7. QSAR Conference.

Bercu JP. 2016. Practical Implementation of (Q)SAR and Expert Review for Compliance with ICH M7 Guidelines. Streamlining Drug Discovery and Development.

Bercu JP. 2016. Impurities: The Good, the Bad, and the Ugly. American College of Toxicology Webinar.

Bercu JP. 2015. Generating AI's and PDE's for Mutagens and Carcinogens per the ICH M7 Guideline. American Association of Pharmaceutical Scientists (AAPS).

Bercu JP. 2015. How OELs and ADEs Develop over the Life Cycle of a Drug. Highly Potent API (HPAPI) Summit.

B. Stanard B, Bercu JP, Hanneman W, Legare ME. 2015. Threshold of Toxicological Concern (TTC) for Anticancer Compounds. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract #201.

Bercu JP, Gombar, VK. 2014. In Silico Methods for Mutagenicity Prediction vis a vis ICH M7 Guidance. Session Chair. American College of Toxicology.

Bercu JP. 2013. Addressing Risks of the Potential Presence of Multiple Genotoxic/Carcinogenic Impurities in Pharmaceuticals. Society of Toxicology.

Bercu JP. 2010. Evaluating Genotoxicity SAR: Experience from Analysis of Pharmaceutical Impurities. Environmental Mutagen Society, Annual Meeting.

Bercu JP, Morton SM, Deahl JT, Gombar VK, Callis CM, Zwickl CM, van Lier RL. 2009. Risk assessment of genotoxic impurities in a pharmaceutical using in silico tools. Toxicology and Risk Assessment Conference.

Bercu JP. 2009. Managing Genotoxic Impurities throughout Development of Pharmaceutical: Control Strategies and Case Studies. Genetic Toxicology Association.

Bercu JP. 2009. Short-Term and Intermittent Exposure to Carcinogens - Current Approaches. Workshop Sponsored by International Life Sciences Institute - Health Environmental and Sciences Institute.

Bercu JP. 2009. The Threshold of Toxicological Concern - Background and Applications. Session Chair. American College of Toxicology.

Hoffman WP, Ness D, Lee C, Bercu JP. 2009. Linking CMC and Toxicology: The Use of Cumulative Carcinogenic Risk for Multiple Genotoxic Impurities Criteria. Midwest Biopharmacueticals Statistics Workshop.

Bercu JP. 2008. Risk assessment of genotoxic and carcinogenic impurities: Current issues and case studies. Int. J. Toxicol. 27(6): 405.

Bercu JP. 2008. Risk Assessment of Genotoxic and Carcinogenic Impurities: Current Issues and Case Studies. American College of Toxicology.

Bercu JP. 2008. Using Genetic Toxicology Information to Evaluate Safety of Impurities and Metabolites for Pharmaceuticals. Society of Toxicology; National Meeting.

Bercu JP. 2008. Risk Management of Genotoxic Compounds in the Manufacture of Pharmaceuticals. Toxicology and Risk Assessment Conference.

Bercu JP, Dobo KL. 2007. Identification and risk assessment of human genotoxic drug metabolites. The Toxicologist. 96(1): 331.

Callis CM, Bercu JP, Moreno MA. 2007. Toxicology and analytical chemistry: An integrated strategy for leachable studies on a polymeric stopper material. Parenteral Drug Association.

Bercu JP, Callis CM, Fiori JM, Meyerhoff RD. 2006. Process to minimize genotoxic impurities in production of a new drug substance. The Toxicologist. 90(1): 179.

Bercu JP, Fiori JM, Meyerhoff RD. 2004. Human health risk assessment for environmental residues of atomoxetine. The Toxicologist. 78(1-S): 152.

Callis CM, Fiori JM, Bercu JP, Meyerhoff RD. 2004. The Threshold of Toxicological Concern (TTC) as an acceptable limit for leachables from polymeric materials into pharmaceutical ingredients. Parenteral Drug Association.

Bercu JP, Smith MA. 2000. Modulation of the benzodiazepine (BZD) receptor/GABA complex affects cell death induced by oxidant stress in Madin Darby canine kidney (MDCK) cells. The Toxicologist. 54(1): 406.

Bercu JP. Gulf Coast Society of Toxicology Meeting. 1999. Modulation of Benzodiazepine (BZD) Receptor/ GABAA Complex Affects Cell Death Induced by Oxidant and Stress in Madin Darbin Kidney (MDCK) Cells.

8. REFERENCES

The following references were used in the preparation of this Environmental Assessment and are generally available. Specific citations from these references may be obtained upon request.

European Chemicals Agency. Guidance on information requirements and Chemical Safety Assessment. Chapter R.16: Environmental exposure assessment 3.0. Helsinki, Finland. February, 2016.

European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP). Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'. [EMA/CHMP/SWP/44609/2010 Rev. 1]. London, England. May, 2016.

Food & Drug Administration (FDA). CFR-Code of Federal Regulations Title 21 [21CFR25.31]. Revised 21 September. 2016.

U. S. Department of Health and Human Services (DHHS), Food & Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologic Evaluation and Research (CBER). Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications. CMC 6. Revision 1. July. 1998.

9. APPENDICES

Appendix 1. Emtricitabine Data Summary Table
Appendix 2. Referenced Study Reports

9.1. Nonconfidential Appendices

Appendix 1. Emtricitabine Data Summary Table

Emtricitabine Data Summary Table	
Physical/Chemical Characterization	
Water Solubility	112 mg/mL
Dissociation Constants	2.65
Octanol/Water partition Coefficient (Log K_{ow}) (OECD 107)	-0.693 (pH 4) -0.670 (pH 7) -0.693 (pH 10)
Vapor Pressure	Presumably non-volatile
Sorption/Desorption (K_{oc}) (OECD 106)	21.1 – 45.6
Depletion Mechanisms	
Hydrolysis	No data available
Aerobic Biodegradation in Water (OECD 301D)	Not readily biodegradable
Photolysis	Absorbs in the UV range, but assumed not to be photolabile
Metabolism	FTC is minimally transformed (13%), most appears unchanged in urine (86%)
Environmental Effects	
Microbial Inhibition **Activated Sludge (OECD 209)**	NOEC ≥ 1000 $mg.L^{-1}$ EC_{50} > 1000 $mg.L^{-1}$
Acute Toxicity Freshwater Green Alga (OECD 201) *Pseudokirchneriella subcapitata*	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$
Water Fleas (OECD 202) *Daphnia magna* Acute Toxicity	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$
Rainbow Trout (OECD 203) *Oncorhynchus mykiss*	NOEC ≥ 110 $mg.L^{-1}$ LC_{50} > 110 $mg.L^{-1}$
Chronic Toxicity Fathead Minnow (OECD 210) *Pimephales promelas* Fish Early Life Cycle	LOEC = 11 $mg.L^{-1}$ NOEC = 6.1 $mg.L^{-1}$
Water Fleas (OECD 211) *Daphnia magna* Reproduction	NOEC ≥ 110 $mg.L^{-1}$ LOEC > 110 $mg.L^{-1}$
Sediment Dwellers (OECD 218) Chironomid Larvae Toxicity	Normalized NOEC ≥ 200 $mg.kg_{dwt}^{-1}$ Normalized LOEC > 200 $mg.kg_{dwt}^{-1}$

9.2. Confidential Appendices

Appendix 2. Referenced Study Reports

This section provides a list of all study reports that have been cited in the present Environmental Assessment and can be accessed via the hyperlinks below.

Cross-reference to Gilead Nonclinical Reports

Study Report Number	Study Title
BA-162-2001	Validation of the Analytical Method for the Determination of Radiolabelled Emtricitabine in Sediment
AD-162-2001	Emtricitabine - Determining the Adsorption Coefficient (Koc) Following OECD Guideline 106
AD-162-2002	Determining the Partitioning Coefficient (n-Octanol/Water) of Emtricitabine by the Flask-shaking Method Following OECD Guideline 107
AD-162-2003	Activated Sludge Respiration Inhibition Test to Emtricitabine Following OECD Guideline 209
AD-162-2004	Emtricitabine – Aerobic and Anaerobic Transformation in Aquatic Sediments Systems Following OECD Guideline 308
1784	Emtricitabine (CAS # 143491-57-0): Ready Biodegradability Evaluation (OECD 301D)
TX-162-2002	Acute Toxicity of Emtricitabine to the Freshwater Green Alga *Pseudokirchneriella subcapitata* Following OECD Guideline #201
TX-162-2003	Acute Toxicity of Emtricitabine to Water Fleas, *Daphnia magna* Under Static Conditions, Following OECD Guideline #202
TX-162-2004	Acute Toxicity of Emtricitabine to Rainbow Trout (*Oncorhynchus mykiss)* Under Static Conditions, Following OECD Guideline #203
TX-162-2005	Early Life-Stage Toxicity Test of Emtricitabine with Fathead Minnow, (*Pimephales promelas*), Following OECD Guideline #210
TX-162-2007	Emtricitabine; Toxicity test with Sediment-Dwelling Midges (Chironomus riparius) Under Static Conditions, Following OECD Guideline 218
TX-162-2006	Emtricitabine – Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Static Renewal Conditions, Following OECD Guideline #211

James Laurenson

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Michael Furness

Digitally signed by Michael Furness
Date: 11/01/2017 09:24:09AM
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LABELING

IQA Review Guide Reference

NDA 210251

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BIKTARVY safely and effectively. See full prescribing information for BIKTARVY.

BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: XXXX

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets
Dosage form, route of administration	tablets, for oral use
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use To replace with the following BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, 50 mg/200 mg/25 mg, for oral use

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with BIKTARVY
Prior to or when initiating BIKTARVY, test patients for hepatitis B virus infection [see Warnings and Precautions (5.1)].

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus [see Warnings and Precautions (5.4)].

2.2 Recommended Dosage
BIKTARVY is a three-drug fixed dose combination product containing 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)].

2.3 Not Recommended in Patients with Severe Renal Impairment
BIKTARVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute [see Use in Specific Populations (8.6)].

2.4 Not Recommended in Patients with Severe Hepatic Impairment
BIKTARVY is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) [see Use in Specific Popoulations (8.7) and Clinical Pharmacology (12.3)].

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)].

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS
Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).
Strengths: in metric system	contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).
Active moiety expression of strength with equivalence statement (if applicable)	50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The tablets are purplish brown, capsule-shaped, film-coated, and debossed with "GSI" on one side and "9883" on the other side.

4. *Section 11 Description*

11 DESCRIPTION

BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

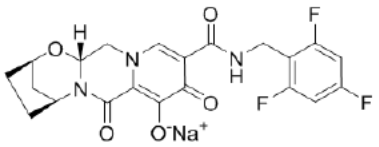
- BIC is an integrase strand transfer inhibitor (INSTI)
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′ - monophosphate.

Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 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 iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Bictegravir: The chemical name of bictegravir sodium is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), (2R,5S,13aR)-.

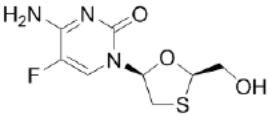
Bictegravir sodium has a molecular formula of $C_{21}H_{17}F_3N_3NaO_5$ and a molecular weight of 471.4 and has the following structural formula:



Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

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

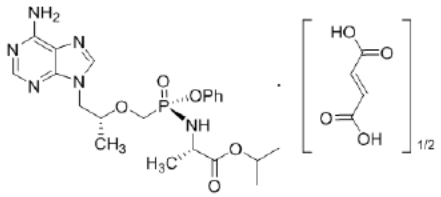
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.2 and has the following structural formula:



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)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a formula weight of 534.5 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
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide)
Dosage form and route of administration	a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 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 iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	BIC is an integrase strand transfer inhibitor (INSTI) FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI). TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.
Chemical name, structural formula, molecular weight	Available
If radioactive, statement of important nuclear characteristics.	NA

Other important chemical or physical properties (such as pKa or pH)	Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C. FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C. 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.

5. *Section 16 How Supplied/Storage and Handling*

HOW SUPPLIED/STORAGE AND HANDLING
BIKTARVY tablets are purplish brown, capsule-shaped, and film-coated with "GSI" debossed on one side and "9883" on the other side. Each bottle contains 30 tablets (NDC 61958-2501-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) [redacted] (b) (4) 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) [redacted] (b) (4)

Store below 30 °C (86 °F).

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

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) [redacted] (b) (4) 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) [redacted] (b) (4)
Available units (e.g., bottles of 100 tablets)	Each bottle contains 30 tablets (NDC 61958-2501-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	BIKTARVY tablets are purplish brown, capsule-shaped, and film-coated with "GSI" debossed on one side and "9883" on the other side.
Special handling (e.g., protect from light)	•Keep container tightly closed. •Dispense only in original container.
Storage conditions	Store below 30 °C (86 °F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	To add Manufacturer/distributor name (21 CFR 201.1(h)(5))

Reviewer's Assessment of Package Insert: ***{Adequate/Inadequate}***

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

[redacted]

2.

Carton Label

(b) (4)

[redacted]

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tradename™ (bictegravir, emtricitabine, tenofovir alafenamide) tablets 50 mg/200 mg/25 mg Acceptable to prominence, font size, and prominence	(b) (4)
Dosage strength	50 mg/200 mg/25 mg And Each tablet contains 50 mg of bictegravir (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate).	
Net contents	30 tablets	
"Rx only" displayed prominently on the main panel	Rx only	
NDC number (21 CFR 207.35(b)(3)(i))	NDC 61958-2501-1	
Lot number and expiration date (21 CFR 201.17)	The space is available. However, it is not indicated if the space is reserved for lot number and expiration date.	
Storage conditions	Store below 30 °C (86 °F) Keep container tightly closed. Dispense only in original container. See package insert for dosage and administration. KEEP OUT OF THE REACH OF CHILDREN	
Bar code (21CFR 201.25)	Available	
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc. Foster City, CA 94404	

	Made in Germany	(b) (4)
And others, if space is available		

Reviewer's Assessment of Labels: ***{Adequate/Inadequate}***

Per 21 CFR 201.17, confirm if the space is available for lot number and expiration date in the proposed container label.

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies:

In highlights of prescribing information, "BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use" should be replaced with "BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, 50 mg/200 mg/25 mg, for oral use."

In Section 16 How Supplied/Storage and Handling, please add names for manufacturer/distributor per 21 CFR 201.1(h)(5).

Per 21 CFR 201.17, confirm if the space is available for lot number and expiration date in the proposed container label.

Overall Assessment and Recommendation:

It is recommended for approval upon the competition of the above changes from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Yong Wang

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

Yong Wang

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Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 11/13/2017 04:54:08PM
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BIOPHARMACEUTICS

Product Background:

NDA: 210251
Submission Type: 505(b)(1) NDA; using a Tropical Disease Voucher (Priority)
Chemical Type: Type 1 NME (for bictegravir), Type 4 New Combination

Drug Product Name / Strength: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF), 50 mg (as bictegravir free base)/ 200 mg/ 25 mg, Immediate-Release (b) (4), Fixed Dose Combination Tablet

Route of Administration: Oral
Recommended Dosage (for treatment of HIV infection in adults): One tablet once daily with or without food

Applicant Name: Gilead Sciences, Inc.

Review Recommendation:
From the Biopharmaceutics perspective, NDA 210251 for B/F/TAF (50 mg/200 mg/25 mg) Tablets is recommended for APPROVAL.

Review Summary:
The proposed QC dissolution method and the revised dissolution acceptance criteria as tabulated below are approved for the routine QC testing of the B/F/TAF (50 mg/200 mg/25 mg) Tablets (submitted under NDA 210251).

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddle)	75 rpm	pH 5.5 (50 mM) citrate buffer, 37 ± 0.5°C	900 mL	For all three APIs: Q = (b) (4)% at 30 min

The proposed to-be-marketed drug product has the same formulation, appearance, and drug product manufacturing process/site, and API suppliers as the Phase 3 clinical/primary stability batches. The proposal to add an alternate drug product manufacturer for commercialization was supported with evidence of comparable *in vitro* dissolution profiles between the test and the reference drug products. Similarly, adequate *in vivo* PK and *in vitro* dissolution profile data are available to support the slight change in formulation of the B/F/TAF (50 mg/ 200 mg /25 mg) Tablets used in clinical development studies.

List Submissions being reviewed:
SDN-2, 6/12/2017 (Original NDA)
SDN-9, 8/3/2017 (Response to Quality Information Request – dissolution)
SDN-10, 8/22/2017 (Response to Quality Information Request - particle size)
SDN-14, 9/28/2017 (Response to Quality Information Request – dissolution)

Concise Description Outstanding Issues Remaining:
None

BCS Designation

Bictegravir (BIC, formerly known as GS-9883-01) is a New Molecular Entity (NME) whereas Emtricitabine (FTC) and Tenofovir Alefamide (TAF) are APIs of approved FDA antiviral drug products.
The Applicant considers the drug substance BIC as exhibiting the characteristics of a BCS-2 (low solubility/high permeability) drug substance. Additionally, the Applicant considers FTC as a BCS-1 (high solubility/high permeability) drug substance, and TAF as a BCS-3 (high solubility/low permeability) drug substance.

Reviewer's Assessment:

Solubility: *Low Solubility for BIC, High Solubility for both FTC and TAF*
BIC exhibits low solubility (per BCS criteria), and pH-independent solubility in media without surfactant. On the other hand, per BCS criteria, both FTC and TAF are highly soluble because < 250 mL volumes of various pH media are anticipated to be sufficient to dissolve the individual labeled amounts of FTC and TAF at 37 °C. When tested individually, the solubility values of BIC, FTC, and TAF in media with pH across the physiologic range were at least 0.1 mg/mL, 100 mg/mL, and 4.7 mg/mL, respectively, at room temperature (~ 20-25 °C). Note that for the treatment of HIV infection in adults, the proposed dosage of the B/F/TAF (50/200/25 mg) Tablet is one tablet orally once daily with or without food.

Permeability: *Low Permeability for BIC and TAF; High Permeability for FTC*
The Clinical Pharmacology Reviewer (Dr. Vikram Arya) confirmed that at least 59% of the administered dose of bictegravir is absorbed, i.e., following administration of an oral dose of 100-mg [^{14}C] BIC under fed conditions, with a 91% recovery rate. The absolute bioavailability of BIC is not known, and so based on the results of the human ADME Study, the permeability of BIC is deemed to be *Low*. Of note, the Applicant states that based on the results of a Caco-2 permeability study, BIC exhibits high permeability with concentration dependent efflux; the efflux ratios were 4.4 and 1.5 at BIC concentrations of 10 µM and 88 µM (solubility limit), respectively. Refer to the Clinical Pharmacology and Pharmacology/Toxicology Reviews for the evaluation of the Caco-2 permeability study results.

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(b) (4)

Dissolution Acceptance Criteria *- REVISED ACCEPTANCE CRITERIA ACCEPTABLE*

For the routine QC testing of the B/F/TAF (b) (4) tablets, the proposed QC dissolution acceptance criteria are "Meet the USP and Ph. Eur. criteria for the amounts of BIC, FTC, and TAF dissolved at 30 minutes when Q is (b) (4)%." Per the Applicant, the proposed dissolution acceptance criterion takes in consideration (1) the immediate-release dosage form of the to-be-marketed drug product, (2) the need to ensure complete disintegration and dissolution within the typical gastric emptying time, (3) the plasma Tmax of the three API's, i.e., 0.5 to 2 hours, and (4) the capability to discriminate between clinically acceptable drug product batches and aberrant tablets.

This Reviewer recommends tightening of the dissolution acceptance criterion to 'Q = (b) (4) % at 30 min' for all three APIs, based on (1) the *in vitro* dissolution profiles of the ee APIs provided for the Phase 3 clinical trial batches which all converged at the 30 minute time point, and (2) considering that this revised dissolution acceptance criterion (Q = (b) (4)% at 30 min for all 3 APIs) is sufficient to reject the aberrant drug product batches as shown in Figures 1 and 2 above. Note that an earlier specification time point (i.e., 15 or 20 min) was not chosen by this Reviewer to avoid/minimize the potential for rejecting B/F/TAF tablet batches with *in vitro* dissolution profiles similar to Phase 3 clinical trial Batches EN1609B and EN1610B. (b) (4)

For the six drug product batches undergoing stability testing, the reported mean dissolution data at 30 min for all three APIs ranged from 95 – 104%, indicating conformance to this Reviewer's recommended dissolution acceptance criterion of 'Q = (b) (4) % at 30 min' over up to 12 months of long-term storage (25°C/60%RH and 30°C/75%RH). Note that the corresponding range of mean dissolution for all three APIs at 30 min was 94% - 103% after storage at 40°C/75%RH for up to 6 months for the same stability batches.

In the 9/18/2017 response to the Biopharmaceutics Information Request dated 9/14/2017, the Applicant agreed to revise the QC dissolution acceptance criterion to 'Q = (b) (4)% in 30 min for all three APIs', and the pertinent NDA documents were updat accordingly.

Bridging of Formulations

Reviewer's Assessment: *ADEQUATE*

The pivotal Phase 3 clinical trials GS-US-380 -1489, -1490, -1844, and -1878 used two (i.e., original and final) formulations of the B/F/TAF [50/200/25 mg] FDC (b) (4) tablets. Additionally, the original formulation was used in the Relative BA and Food-Effect Study GS-US-141-1233, and various drug-drug interaction studies (GS-US-380 -1999, -3908, -3909, and -4270). Note that the original formulation is different from the final formulation only in terms of the (b) (4) Both *in vivo* PK and *in vitro* dissolution profile data are available to bridge the final formulation to the original formulation used in these pivotal Phase 3 and Phase 1 clinical studies. Based on the population PK analysis conducted by the Pharmacometrics Reviewer (Dr. Ada Zhuang), it was confirmed that "formulation" was not a significant covariate of BIC pharmacokinetics. Likewise, the Applicant's own Population PK analysis did not find "formulation" to be a significant covariate of TAF pharmacokinetics. Additionally, the original formulation batches (EN1503B and EN1504B) exhibited very rapid dissolution profiles in the proposed QC medium, similar to the final formulation (pilot scale) batches used in the Phase 3 clinical trials.

The to-be-marketed drug product and the final formulation used in the Phase 3 clinical trial and the registration drug product batches have the same appearance, formulation, and manufacturing process. The drug product manufacturing site is also the same for the designated commercial formulation and the final formulation used in the Phase 3 clinical trial, however; the Applicant has proposed to add an alternate drug product manufacturing site. Using the proposed QC dissolution method, it was observed that the pilot-scale and process scale-up batches produced by (b) (4) and used as the final formulation in the Phase 3 clinical trials exhibited rapid to very rapid dissolution for BIC, FTC and TAF, and the batches produced by the alternate/additional proposed commercial Drug Product Manufacturer (Gilead/Ireland) exhibited generally very rapid dissolution for all three APIs. Overall, the dissolution profile data provided support the addition of the alternate Drug Product Manufacturing site.

With respect to the BIC drug substance, the proposed commercial manufacturers (Gilead/Canada, and (b) (4)) are the same as used in the manufacture of the Phase 3 clinical batches. Additionally, the proposed commercial FTC and TAF drug substance and intermediate suppliers were either the same as used in the manufacture of the Phase 3 clinical batches or (per the FDA Facility Reviewer) had been previously qualified under cross-referenced NDA 207561 (original) and NDA 021500/Suppl-1.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:
Gerlie Gieser, Ph.D., 9/29/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Elsbeth Chikhale, Ph.D., 10/29/2017

Gerlie Gieser

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Elsbeth Chikhale

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

Final Risk Table for Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF (NDA #210251)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**		Acc	
Physical stability (solid state)		**M**	Previous experience with FTC/TAF. Stability results for BIC alone	Acc	
Content uniformity		**M**	Content uniformity release testing per <905> (b) (4) [redacted] was performed	Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**	Dissolution method had discriminating power and the Applicant has revised acceptance criteria	Acc	
Tablet water content		**L**		Acc	
Drug Product Impurity Control		**M**	Controlled by release and stability specifications; stability results also indicate this risk is mitigated	Acc	

Andrei
Ponta

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QUALITY ASSESSMENT

Recommendation: Pending

NDA 210251

Review #1

Drug Name/Dosage Form	Biktarvy (Bictegravir, Emtricitabine, and Tenofovir Alafenamide) tablets
Strength	50 mg Bictegravir / 200 mg Emtricitabine / 25 mg Tenofovir Alafenamide
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED		DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New NDA	SD #0000	*12-Jun-2017*	All
Proprietary Name Review	SD #0001	*20-Jun-2017*	All
Quality Response to IR	SD #0007	*3-Aug-2017*	Drug Substance
Quality Response to IR	SD #0008	*22-Aug-2017*	Biopharmaceutics
Quality Response to IR	SD #0012	*28-Sep-2017*	Drug Substance
Quality Response to IR	SD #0014	*6-Oct-2017*	Biopharmaceutics, Drug Product, and EA
Quality Response to IR	SD #0016	*19-Oct-2017*	Drug Substance and Laboratory
Labeling	SD #0017	*1-Nov-2017*	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Dr. Gaetan Ladouceur	Dr. Ben Stevens
Drug Product	Dr. Yong Wang	Dr. Balajee Shanmugam
Process	Dr. Ying Wang	Dr. Steven Frisbee
Microbiology	Dr. Ying Wang	Dr. Steven Frisbee
Facility	Dr. Frank Wackes	Dr. Christina Capacci
Biopharmaceutics	Dr. Gerlie Geiser	Dr. Elsbeth Chikhale
Environmental Assessment	Dr. James Laurenson	-
Laboratory (OTR)	Dr. Priyanka Chistranshi	Dr. Laura Pogue
ORA Lead	-	-
Regulatory Business Process Manager	Dr. Luz Rivera	-
Application Technical Lead	Dr. Andrei Ponta	-

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
NA	Type II	-	-	-	-	-
Various	Type III *(if applicable)*	Various	(b) (4)	Adequate	See DP review	-
Various	Type IV *(if applicable)*	Various		Adequate	See DP review	-
NA	Other	-	-	-	-	-

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
#0000 #0627	NDA 21752	Emtricitabine drug substance and Environmental Analysis
#0000	NDA 207561	Tenofovir Alafenamide drug subsistence
#0001	IND 53971	Emtricitabine
#0001	NDA 21500	Emtricitabine
#0001	NDA 21896	Emtricitabine
#0001	IND 52849	Viread (Tenofovir)
#0001	IND 51285	Viread (Tenofovir)
#0001	NDA 21356	Viread (Tenofovir)
#0001	IND 103093	Stirbild
#0001	NDA 203100	Stirbild
#0001	NDA 201283	Cobicstat
#0001	NDA 202123	Complera
#0001	NDA 208215	Descovy
#0001	NDA 208351	Odefsey
#0001	IND 06737	TAF
#0001	NDA 208464	Vemlidy
#0001	NDA 208341	Epclusa
#0001	NDA 209195	SOF/VEL/VOX
#0001	IND (b) (4)	Bictegravir
#0001	IND 125589	B/F/TAF
#0001	IND 06761	Truvada
#0001	IND 111007	Genvoya

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharm/Tox	NA			
CDRH	NA			
Clinical	NA			
Other (Method Verification)	Ongoing	NA	8-Nov-2017	Dr. Priyanka Chistranshi

Executive Summary

I. Recommendations and Conclusion on Approvability

At the present time, a final recommendation cannot be made from the product quality perspective as the evaluation of the manufacturing facilities is on-going. Specifically, there is a pOAI alert for [redacted] (b) (4) the emtricitabine drug substance manufacturer. Additionally, there is an ongoing (Nov. 6th –Nov. 10th) PAI/GMP inspection for the primary packaging and labeling site Gilead Sciences Inc. The outcome of the facilities inspection will be captured in an Addendum.

The remaining drug product quality aspects of this application are acceptable.

II. Summary of Quality Assessments

A. Product Overview

This NDA submission is accompanied by a Tropical Disease Voucher and has been reviewed as a priority review.

The proposed drug product, Biktarvy, is a fixed dose combination (FDC) immediate release tablet containing bictegravir (BIC) 50 mg, emtricitabine (FTC) 200 mg, tenofovir alafenamide (TAF) 25 mg. The drug product is a [redacted] (b) (4) BIC/FTC/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. The tablets are approximately 15 mm in length and 8 mm in width. The container closure system consists of a 100 mL, white, high-density polyethylene (HDPE) bottle containing 30 tablets.

The drug product is indicated for the treatment of HIV-1 infection in adults who are HIV-1 treatment-naïve or virologically-suppressed with no known mutations associated with resistance to the individual components of the drug product (BIC/FTC/TAF). The administration is one tablet daily with or without food. The drug product is intended for chronic use unless resistance develops.

Proposed Indication(s) including Intended Patient Population	Biktarvy is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen.
Duration of Treatment	One tablet taken once daily with or without food. The drug product is for chronic use unless resistance develops.
Maximum Daily Dose	One tablet (50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide).
Alternative Methods of Administration	Oral use only.

B. Quality Assessment Overview

The proposed drug product, Biktarvy, is a fixed dose combination (FDC) immediate release tablet containing bictegravir (BIC) 50 mg, emtricitabine (FTC) 200 mg, tenofovir alafenamide (TAF) 25 mg.

At this time, a recommendation cannot be made for this application as the facility inspection is ongoing. There is currently a pOAI alert for [redacted] (b) (4)., the emtricitabine drug substance manufacturer. Additionally, there is an ongoing (Nov. 6th –Nov. 10th) PAI/GMP inspection for the primary packaging and labeling site Gilead Sciences Inc. The remaining drug product quality aspects of this application are acceptable.

The BIC drug substance is a new molecular entity (NME). The Applicant considers BIC a BCS 2 drug substance (low solubility/high permeability). [redacted] (b) (4) that is an off-white to yellow solid. The Applicant monitors nine related substances which are controlled at various levels in the drug substance specifications. The proposed acceptance criteria of these impurities have been evaluated by the Pharm./Tox. review team and were found to be acceptable. BIC has been shown to be stable under the long-term studies (12 months) and accelerated conditions (6 months).

The Applicant cross references drug substance information for FTC from NDA 21752 (Truvada®, Gilead), which was approved by the Agency on 2-Aug-2004. The Applicant considers FTC as a BCS 1 drug substance (high permeability/high solubility). [redacted] (b) (4)

The Applicant cross references drug substance information for TAF from NDA 207561 (Genvoya®), which was approved by the Agency on 5-Nov-2015. The Applicant considers TAF as a BCS 3 drug substance (low permeability/high solubility). TAF [redacted] (b) (4)

The drug product is a [redacted] (b) (4) tablet containing the three drug substances and compendial excipients, with film coating [redacted] (b) (4). [redacted] (b) (4)

The manufacturing process has been extensively developed, adequately described and controlled. Note that the formulation and manufacturing process for (b) (4) is identical to that of Gilead's approved product, Descovy (NDA #208215).

The commercial drug product is to be manufactured at two sites: (b) (4) and Gilead Sciences Ireland UC. The Applicant has provided release and stability results for drug product batches manufactured at both sites. The addition of the Gilead Sciences Ireland site is also supported with evidence of comparable *in vitro* dissolution profiles between the test and the reference drug products.

The Applicant has manufactured 14 drug product batches to date, 11 of which were manufactured at the (b) (4) site while the remaining three were manufactured at Gilead Sciences Ireland UC. The Applicant has used drug substance batches manufactured from all of the proposed commercial manufacturing sites in the manufacture of the drug product. All drug product batches manufactured to date met the propose release specifications.

Gilead has provided twelve months of stability data for three registration batches manufactured at (b) (4) and three months of stability data for three batches manufactured at Gilead Sciences Ireland UC. The majority of parameters remain within specifications with no trend being apparent. The drug product shows little to no variation in BIC and FTC assay. Slight drops in TAF assay (0.3 - 1.6%) have been observed but this is within the proposed specifications. The drop in assay is associated with an increase in impurities but these likewise remain within specifications. Based on the stability data, the proposed shelf life of 24 months is acceptable when stored below 30°C.

The Initial Risk Table identified four aspects as moderate risk: physical stability (b) (4) content uniformity; dissolution; and drug product impurity controls.

The physical and chemical compatibility of FTC and TAF have been previously established during development of Genvoya, Descovy, and Odefsey. Formulations containing FTC and TAF in combination have exhibited adequate FTC and TAF chemical stability. The Applicant also provided physical and chemical stability data for BIC tablets demonstrating that the drug substance remains stable.

The risk with content uniformity is mitigated by (b) (4) testing per USP <905> on release of the drug product. Additionally, the Applicant has performed (b) (4) testing as part of the manufacturing process development.

The dissolution method has been evaluated and was shown to have discriminating power for intentional alterations in the tablet formulation, including being able to detect different forms of BIC. The Applicant has also revised the dissolution acceptance criterion (Q = (b) (4)% at 30 minutes) ensuring that the criterion is sufficient to reject aberrant drug product batches.

The risk of drug product impurities is primarily associated with TAF related substances. However, the impurities have been qualified by the Applicant at the proposed limit levels and the stability data to date demonstrates that the drug product remains well within these levels.

The drug product container closure system consists of a 100 mL, white, high-density polyethylene (HDPE) bottle and a continuous thread, child-resistant polypropylene (PP) screw cap lined with an induction-sealed, aluminum foil liner. Each bottle contains 30 tablets and either a [redacted] (b) (4) containing a three gram silica gel desiccant, and polyester coil packing material.

The drug product is also to be available as part of the Gilead access program. The tablets to be part of the access program are identical to the proposed commercial drug product. The only difference is the packaging has [redacted] (b) (4) on the container label.

The Applicant has submitted claims for categorical exclusion for BIC and TAF per 21 CFR 25.15(a) and 21 CFR 25.31(b). A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment has been submitted for the categorical exclusions, per 21 CFR 25.15(a). Gilead has prepared an environmental analysis for FTC evaluating the potential environmental impact from the use and disposal of this product. Based on the information provided, the Agency is issuing a finding of no significant impact and thus an environmental impact statement will not be prepared.

C. Special Product Quality Labeling Recommendations (NDA only)

The following recommendations were conveyed to the OND PM for consideration as the labeling is not yet finalized:

1. In Section 16 How Supplied/Storage and Handling, please add names for manufacturer/distributor per 21 CFR 201.1(h)(5).
2. Per 21 CFR 201.17, confirm if the space is available for lot number and expiration date in the proposed container label.

D. Final Risk Assessment (see Attachment)

Andrei Ponta, Ph.D.

Application Technical Lead for NDA 210251

Date: 14-Nov-2017

Andrei Ponta

Digitally signed by Andrei Ponta
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ENVIRONMENTAL

IQA Review Guide Reference

R Regional Information

Summary: The applicant submitted claims for categorical exclusion for bictegravir (BIC) and tenofovir alafenamid (TAF) from the requirement to prepare an environmental assessment (EA) under 21 CFR 25.15(a) and 21 CFR 25.31(b). A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment was submitted for the categorical exclusions, per 21 CFR 25.15(a). FDA requested additional information and a correction. Upon review, FDA determined that the applicant cited the appropriate exclusion and provided the required statement of no extraordinary circumstances. The claims and updated supporting information were found to be acceptable. The applicant also submitted an EA for emtricitabine (FTC) under 21 CFR 21.14(a) and 21 CFR 25.40. FDA concluded that (1) the EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment and (2) the proposed action does not appear to significantly affect the environment, and thus a finding of no significant impact (FONSI) has been filed.

Environmental

Initially, the applicant submitted

1. Claims for a categorical exclusion for bictegravir (BIC) and tenofovir alafenamid (TAF) from the requirement to prepare an environmental assessment (EA) under 21 CFR 25.15(a) and 21 CFR 25.31(b) and

2. An EA for emtricitabine (FTC, for 2'-deoxy-5-fluoro-3'-thiacytidine) under 21 CFR 21.14(a) and 21 CFR 25.40.

A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment was submitted for the categorical exclusions, per 21 CFR 25.15(a).

Categorical Exclusions

The claims for a categorical exclusion for BIC and TAF was submitted on the basis of a less than 1 part per billion (ppb) level of expected introduction concentration (EIC) at the point of entry into the aquatic environment. Specifically, the BIC EIC was (b) (4) ppb, and the TAF EIC was (b) (4) ppb.

FDA responded that the claim for an exclusion for TAF might not be acceptable because the active moiety, tenofovir, is the same as that of the previously approved tenofovir disoproxil fumerate (TDF), which currently has an EIC of ≥ 1 ppb and thus does not meet

the < 1 ppb requirement. FDA noted that if there will be an increase in tenofovir use due to approval of this application, with an overall tenofovir EIC of ≥ 1 ppb, then an EA would be required. Alternatively, FDA noted, if there will be no change or a decrease in the use of tenofovir, then a categorical exclusion under 21 CFR 25.31(a) (no increased use) would be appropriate. If an EA is required, FDA stated that the environmental risk assessment (ERA) that the applicant has submitted to the European Medicines Agency (EMA), modified as needed to reflect new information, including the expected environmental concentrations in the US, would appear to be appropriate.

The applicant responded and agreed that a TDF EA submission was provided on January 24, 2012, where the EIC was > 1 ppb and thus greater than the threshold for categorical exclusion under 21 CFR 25.31(a)[sic] based on yearly production estimates of TDF (Section 1.12.14, Environmental Analysis, NDA 021356/SN0673). (FDA assumes that reference to 21 CFR 25.31(a), which address the no-increased-use exclusion, was meant to be 21 CFR 25.31(b), which addresses the 1 ppb exclusion.) Both TDF and TAF are prodrugs of the active moiety, tenofovir, the applicant noted. Specifically, conversion of TDF and TAF *in vivo* makes tenofovir a relevant species for consideration of the EIC.

The applicant then conducted an analysis to determine if tenofovir would indeed exceed the EIC threshold of 1 ppb for a categorical exclusion from both TDF and TAF. The EIC of TDF provided in 2012 was calculated to be (b) (4) ppb based on an annual production estimate of (b) (4) kg/year (Section 1.12.14, Environmental Analysis, NDA 021356/SN0673). However, the applicant notes that TDF's molecular weight of 635.32 g/mol is substantially more than that of tenofovir, 287.21 g/mol, which would result in (b) (4) kg/year for tenofovir. TAF is also a prodrug, with a molecular weight of 534.50 g/mol and an estimated annual production of (b) (4) kg/year (NDA 210251, section 1.12.14, Environmental Analysis). The amount of relative contribution of active tenofovir in TAF thus would be (b) (4) kg/year. The total tenofovir contribution from a combination of TDF and TAF production in turn would be (b) (4) kg/year, and the resulting EIC would be (b) (4) ppb (i.e., < 1 ppb). The applicant also notes that the production of TDF has been declining and for 2017 is estimated at (b) (4) kg/year, which would result in an EIC for tenofovir of (b) (4) ppb. Either way, the categorical exclusion per 21 CFR 25.31(b) for tenofovir would be appropriate.

Environmental Assessment

The EIC for FTC was calculated by the applicant at approximately 1.13 ppb. Because this exceeded the categorical exclusion limit of 1 ppb EIC, the applicant provided a cross reference to the revised FTC EA submitted previously (FTC and TDF, NDA 021752, Section 1.12.14, Environmental Analysis, SN 0627, dated June 2, 2017). This EA began with a Tier 1 and 2 assessment, per FDA guidance, and concluded that Tier 3 testing for chronic toxicity was not needed. Tier 3 data were available, however, and therefore the applicant proceeded with the Tier 3 assessment.

The applicant noted that the majority of FTC (1) will be excreted by patients, (2) is unlikely to bind to sewage solids, and (3) is not readily biodegradable. Thus, a

conservative/protective assumption that would be used is that the EIC, Expected Environmental Concentration (EEC), and Maximum Expected Environmental Concentration (MEEC) for FTC are similar, and thus the EA will use an MEEC of 1.13 ppb (or µg/L).

The effects of FTC on the early life stages of fish was investigated with fathead minnows according to OECD Guideline 210, "Fish, Early-Life Stage Toxicity Test". The lowest-observed-effect concentration (LOEC) was 11 mg/L, and the no-observed-effects concentration (NOEC) was determined to be 6.1 mg/L. Comparing this to the MEEC results in a margin of safety of approximately 5,000.

The effects of FTC on the reproduction of *Daphnia magna* were investigated, according to OECD Guideline 211, "Daphnia magna Reproduction Test". The NOEC for reproduction was determined to be ≥ 110 mg/L, the highest dose, and thus no LOEC could be determined. Comparing this to the MEEC results in a margin of safety of approximately 97,000.

The effects of FTC on the pre-emergent aquatic early life stages of the insect *Chironomus riparius* were investigated, according to OECD Guideline 218, "Sediment Water Chironomid Toxicity Test Using Spiked Sediment". The overall NOEC was determined as ≥ 38 mg/kg-dry weight (dw), the highest dose. Based on EMA guidelines, the applicant converted this NOEC into standard sediment with an organic carbon content of 10%, or 200 mg/kg-dw. Comparing to the calculated sediment concentration derived from the MEEC, or 9.2 µg/kg-dw, results in a margin of safety of approximately 22,000.

Reviewer's Assessment:

Categorical Exclusions

The specific claims for categorical exclusions for the EIC for BIC and the corrected EIC for tenofovir, under 21 CFR 25.31(b), are appropriate for the estimated concentrations. A statement of no extraordinary circumstances, per 21 CFR 25.15(a), was included with the claims.

Given BIC is an NME, FDA conducted additional analysis by utilizing a fish plasma model (FPM; per Nallani et al., 2016 and Huggett et al., 2003) to help screen for aquatic environmental risk. FDA used a therapeutic concentration of 5.1 µg/mL (Table 23, "fasted" food effect, CTD section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods), a predicted log D value of 1.35 (www.chemspider.com), and an environmental concentration of (b) (4). The resulting FPM effects ratio (ER) was 11,800, which is greater than the ratio of 1,000 recommended by Huggett et al., 2003, thus indicating little concern for this substance. In addition, FDA examined an assessment of a claim for categorical exclusion of a previous integrase strand-transfer inhibitor, elvitegravir, for NDA 203100. FDA found that based on a variety of analyses, the EIC of (b) (4) ppb for elvitegravir did not indicate the potential for extraordinary circumstances. While (b) (4) ppb is only about 25% of the EIC for BIC, the margin of safety of toxicity data for elvitegravir was approximately

four orders of magnitude, and thus this difference in concentration is insignificant. Thus, the claim for a categorical exclusion from an EA is acceptable.

Tenofovir is not an NME, and because it had been estimated at > 1 ppb previously, an EA had been conducted. This EA also was conducted under NDA 203100 and resulted in a finding of no significant impact (FONSI). The environmental concentration used in that EA was more than double the current concentration reflected in this claim for a categorical exclusion from an EA. Given the FONSI at the higher concentration, this current concentration also is found to not indicate any potential for extraordinary circumstances. FDA also conducted an FPM analysis for tenofovir as with BIC, in part to further validate FPM. FDA used a therapeutic concentration of 0.21 µg/mL (Table 3, Cmax, CTD section 2.5, Clinical Overview), a predicted log D value of -3.55 (www.chemspider.com), and an environmental concentration of (b) (4) ppb. The resulting FPM ER was 440,000, which is substantially greater than the ratio of 1,000 recommended by Huggett et al., 2003, thus indicating little concern for this substance. Given the results of the EA and FPM, the claim for a categorical exclusion from an EA is acceptable.

Environmental Assessment

The main goals of this review of the FTC EA, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

The EA for FTC contains sufficient information to enable a determination of whether the proposed action may significantly affect the quality of the human environment. The data appear to be accurate and objective. This assessment is considered worst-case because the calculation of the EIC does not take into consideration of (1) metabolism, (2) degradation during wastewater treatment, or (3) dilution, degradation, or removal in surface water. FDA expects that an EEC would be more than an order of magnitude below the EIC, thus adding an order of magnitude to the already substantial margins of safety noted in the assessment. FDA also conducted an FPM analysis as with BIC, in part to further validate FPM. FDA used a therapeutic concentration of 2.1 µg/mL (Table 3, Cmax, CTD section 2.5, Clinical Overview), a predicted log D value of -0.9 (www.chemspider.com), and an environmental concentration of 1.13 ppb. The resulting FPM ER was 53,000, which is substantially greater than the ratio of 1,000 recommended by Huggett et al., 2003, thus indicating little concern for this substance. Given the results of the EA and FPM, FDA agrees that FTC poses no significant environmental risk via this application.

References

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential

impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. Comparison of Measured and Predicted Bioconcentration Estimates of Pharmaceuticals in Fish Plasma and Prediction of Chronic Risk. Bulletin of environmental contamination and toxicology, 96(5), 580-584.

Primary Environmental Reviewer Name and Date: James Laurenson, 10/31/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 11/3/2017

James Laurenson

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Michael Furness

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Finding of No Significant Impact

NDA 210251 Bictegravir, Emtricitabine, Tenofovir Alafenamide (BIC, FTC, TAF) Tablet, 50/200/25 mg

Food and Drug Administration
Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

Gilead Sciences (Gilead) requests approval of NDA 210251 for the treatment of HIV-1 infection. The product is a tablet with BIC, FTC, and TAF in combination in the following doses: 50, 200, and 25 mg, respectively. BIC and TAF have been categorically excluded from an environmental assessment (EA). FTC, along with TAF, forms a nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone.

In support of its application, Gilead prepared an EA for FTC (attached). This EA evaluates the potential environmental impact from the use and disposal of this product. The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and additional information, and has carefully considered the potential environmental impact due to approval of this application. Based on the CDER review of the entirety of this information, FDA has determined that approval of the present application for is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachments: May 25, 2017, Environmental Assessment

SECTION 1.12.14
ENVIRONMENTAL ANALYSIS

EMTRICITABINE

GILEAD SCIENCES, INC.

25 May 2017

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
AR	applied radioactivity
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
CFR	Code of Federal Regulations
DNA	deoxyribonucleic acid
DT_X	disappearance time for an X% reduction
EA	Environmental Assessment
EC_{xx}	XX% effective concentration
FDA	(United States) Food and Drug Administration
FTC	emtricitabine, Emtriva®
hr	hour
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug (Application)
K_d	adsorption coefficient for activated sludge
K_{oc}	adsorption coefficient for organic carbon
K_{ow}	octanol water partition coefficient
LC_{50}	median lethal concentration
L	Liter
MEEC	Maximum Expected Environmental Concentration
mg	Milligram
min	minute
NDA	New Drug Application
NEPA	National Environmental Policy Act
NOEC	no obvserved effect concentration
OECD	Organisation for Economic Co-operation and Development
pKa	acid dissociation constant
POTW	publicly owned treatment works
ppb	part per billion
RCE	Request for Categorical Exclusion
SFO	single first-order
STP	sewage treatment plant
UV	ultraviolet light

1. ENVIRONMENTAL RISK ASSESSMENT

1.1. Date

May 24, 2017

1.2. Name of Applicant/Petitioner

Gilead Sciences, Inc.

1.3. Address

333 Lakeside Drive
Foster City, CA 94404

2. DESCRIPTION OF PROPOSED ACTION

2.1. Requested Approval

Gilead Sciences, Inc. (Gilead) has previously filed and received approval of a New Drug Application (NDA) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emtricitabine (FTC) as a stand-alone medication (NDA#s 021500, and 021896) and in combination with other HIV medications (NDA#s 021937, 202123, 208215, 207561, 208531, 203100, and 021752). As part of the general correspondence for NDA 021752, an updated Environmental Assessment for FTC is being submitted pursuant to 21 CFR part 25 to support a new marketing application for bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) tablet (NDA 210251) {Food & Drug Administration (FDA) 2016}.

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process. FDA's regulations in 21 CFR Part 25 specify that environmental assessments (EAs) must be submitted as part of certain NDAs, abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions (see 21 CFR 25.20), unless the action qualifies for categorical exclusion {Food & Drug Administration (FDA) 2016}.

FTC is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following is submitted according to the requirements under the Food and Drug Administration Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, July, 1998, CMC 6, Revision 1 ("FDA Guidance Document") {U. S. Department of Health and Human Services (DHHS) 1998}. In addition to meeting the FDA Guidance Document requirements Gilead has conducted additional environmental studies as part of their product stewardship of FTC and submits these data pursuant to 21 CFR Part 25 {Food & Drug Administration (FDA) 2016}. Gilead requests continued approval of the use of FTC as requirements under the Guidance and per regulatory requirements for environmental assessment have been met as follows.

2.2. Need for Action

FTC is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination.

2.3. Locations of Use

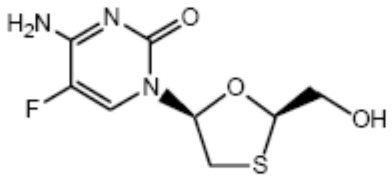
FTC is administered orally and may be used by individuals throughout the United States (US) in hospitals, clinics, and/or homes. It is not expected to be concentrated in any particular geographic region.

2.4. Disposal Sites

In US hospitals, pharmacies or clinics, empty or partially empty bottles will be disposed of according to hospital, pharmacy or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

3. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

3.1. Physical and Chemical Properties

Established Name:	Emtricitabine
Brand/Proprietary Name/ Tradename:	Emtricitabine is used in several brand name products including Stribild®, Odefsey®, Descovy®, Genvoya®, Atripla®, Truvada®, and Emtriva®
Chemical Names:	5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine (IUPAC) 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S* yl)-(1*H*)-pyrimidin-2-one (CAS)
Chemical Abstracts Service (CAS) Registration Number:	143491-57-0
Molecular Formula:	$C_8H_{10}FN_3O_3S$
Molecular Weight:	247.2
Chemical Structure:	

4. ENVIRONMENTAL ISSUES

4.1. Environmental Fate of Released Substances

4.1.1. Identification of Substances of Interest

FTC is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. FTC is minimally transformed (13%), most appears unchanged in urine (86%). The biotransformation of FTC includes oxidation of the thiol moiety to form the 3′-sulfoxide diastereomers (ca. 9% of dose) and conjugation with glucuronic acid to form 2′-O-glucuronide (ca. 4% of dose).

Due to the high proportion of parent excreted, metabolism is considered minimal and not considered further here. A total residue approach is adopted for this risk assessment, where 100% of the dosed FTC is assumed to be excreted unchanged.

The excipients are inert substances which have no pharmacological or toxicological effects and therefore, this assessment will focus on the environmental impact of the active ingredient only.

4.1.2. Physical and Chemical Characterization

The physical and chemical properties of FTC that are environmentally relevant are summarized as follows, and in Appendix 1: Emtricitabine Data Summary Table.

Water Solubility: 112 mg/mL

Dissociation Constants: $pK_a = 2.65$

Partition Coefficient$_{(n\text{-octanol/water})}$: $\log K_{ow} = -0.693$ (pH 4), -0.670 (pH 7), -0.693 (pH 10)

The partition coefficient (*n*-octanol/water) was determined using the flask-shaking method following OECD Guideline 107 and according to Good Laboratory Practices (GLP) (AD-162-2002).

Adsorption Coefficient: K_d (activated sludge) = 5.97 – 12.9
K_{oc} (organic carbon) = 21.1 – 45.6

The adsorption coefficient for FTC was determined following the OECD Guideline 106 and according to GLP (AD-162-2001). It was concluded that FTC does not significantly absorb to activated sludge.

Vapor Pressure: Assumed to be nonvolatile

4.1.3. Environmental Depletion Mechanisms

Ultraviolet-Visible Absorption Spectrum: Absorbs in the UV range, assumed not to be photolabile

Hydrolysis: No data available

Aerobic Biodegradation in Water: Not considered readily biodegradable

FTC was tested to assess its degree of ready biodegradability using the procedure outlined in the OECD guideline 301D and according to GLP for the "Ready Biodegradability Closed Bottle Test" (Report 1784). The results indicate that FTC is not readily biodegradable under the conditions tested.

Aerobic and Anaerobic Transformation in Aquatic Sediment Systems: >10% AR associated with sediment from Day 2; System DT_{50} 36-151 days; No significant metabolites formed.

A GLP study was conducted to assess the degradation of [^{14}C]-FTC in natural water-sediment systems. The rate of aerobic and anaerobic transformation of parent [^{14}C]-FTC was studied at a concentration of 1.0 mg/L in darkness at 20 ± 2ºC for 100 days in two aerobic and anaerobic sediments varying in pH, textual characteristics, organic matter content and microbial content. The study was conducted according to OECD Guideline 308 and according to GLP (AD-162-2004).

Under aerobic water/sediment conditions, FTC degraded at a moderate rate. FTC decreased from an average of 102.9 and 106.7% applied radioactivity (AR) on day 0 to 66.0 and 14.5% AR at study termination (day 100) for the aerobic sandy loam and sand sediments, respectively. 11.7% and 54.3% of applied radioactivity was converted to $^{14}CO_2$ in the sandy loam aerobic and sandy aerobic sediments, respectively.

The whole system disappearance time for a 50% reduction (DT_{50}) and 90% reduction (DT_{90}) was calculated using single first-order (SFO) kinetics, as summarized in below. The primary FTC degradation product was CO_2 and no significant metabolites were formed.

Table 1. Aerobic Total System Degradation Kinetics

System	Compartment	Model	K (days^{-1})	DT_{50} (days)	DT_{90} (days)
Taunton River (Sandy Loam Sediment)	Total System	SFO	-0.0046	150.7	500.7
Weweantic River (Sandy Sediment)	Total System	SFO	-0.0193	35.91	119.3

4.1.4. Environmental Concentrations

The metabolism of FTC will result in excreted drug substance being introduced into the environment primarily through municipal sewage treatment plants (STPs) or septic tanks.

Environmental Introduction Concentration (EIC): The EIC entering the aquatic environment from patient use is calculated without including consideration of metabolism or environmental depletion mechanisms that occur in the waste treatment process. The EIC from patient use is based on the highest annual quantity of the active moiety expected to be produced for use during the next five years; the quantity used in all dosage forms and strengths included in this application; and the quantity used in related applications for FTC.

The calculation of the EIC for the aquatic environment assumes all drug products produced in a year are used and enter the publicly owned treatment works (POTWs), even distribution throughout the US per day, and no metabolism or depletion mechanisms. The EIC was calculated using the following formula from the FDA Guidance Document as follows:

EIC-Aquatic (ppb) = A × B × C × D

where

A = It is expected that FTC will not exceed 50,000 kg/year
B = $1/1.214 \times 10^{11}$ liters/day per day entering publicly owned treatment works (POTWs)
C = year/365 days
D = 10^9 µg/kg (conversion factor)

Using this calculation, the EIC from patient use of FTC is approximately 1.13 ppb.

Because FTC is not readily biodegradable (to CO_2), a conservative/protective assumption of this environmental risk assessment is that the EIC, Expected Environmental Concentration (EEC) and Maximum Expected Environmental Concentration (MEEC) for FTC are similar.

In summary, based on the estimated production data, the MEEC is 1.13 µg/L (1.13 ppb) which requires a (full) Environmental Assessment and not a Request for Categorical Exclusion (RCE) from a full Environmental Assessment under the FDA Guidance Document.

4.1.5. Summary of Environmental Fate of the Substance

The data available suggests that the majority of dosed FTC will be excreted by patients and hence the total dose is representative of the loading to STPs.

Once in municipal STPs, the available data suggests FTC will not be rapidly degraded and is unlikely to bind to sewage solids, which are removed after settling. The adsorption coefficient is sufficiently low to suggest that FTC will not reach the terrestrial soil environment, through the route of spreading of sewage sludge on agricultural land.

Once emitted to surface water, FTC appears to partition to sediment over time. If present in sediment, FTC has variable rates of biodegradation, seeming to be somewhat recalcitrant in sandy loam sediment but fairly well mineralized in sand sediment. Formation of non-extractable residues and mineralization appears to be the major route of removal from sediment/water systems.

The estimated log K_{ow} values indicate that FTC is not lipophilic across the pH range of 4 – 10, which is considered to the pH range which encompasses most environmental situations, as such potential for bioconcentration is low.

As the MEEC exceeded 1 ppb, as per the FDA Guidance Document, an evaluation of the environmental effects of FTC was performed including an assessment of risk based on the MEEC and comparison to Assessment Factors as per the FDA Guidance Document. Based on the fate and effects testing, the environmental impact focused on sewage treatment microbes, acute and chronic aquatic species, and sediment species.

4.2. Environmental Effects of Released Substances

A tiered approach to environmental effects testing of FTC as per the FDA Guidance Document, including a risk assessment evaluation compared to Assessment Factors. As FTC partitions to water based on the above data, effects of released substances on aquatic organisms was conducted for potential acute and chronic effects.

4.2.1. Acute Toxicity (Tier 1 and 2)

4.2.1.1. Sewage Microorganisms

A GLP respiratory inhibition study was conducted with FTC (Lot No. PP-0053-5044, purity of 99.8%) according to OECD Guideline 209, “Activated Sludge, Respiration Inhibition Test” (1993) to determine the concentration which would potentially inhibit the respiratory activity of sewage treatment plant (STP) activated sludge microorganisms (AD-162-2003).

Methods

FTC was tested at concentrations of 0.1, 1.0, 10, 100 and 1000 $mg.L^{-1}$ and 3,5-dichlorophenol was also assayed as a positive control to ensure test validity. Duplicate control vessels were also included in the test.

Prepared vessels were aerated for 3 h, after which dissolved oxygen concentrations were measured for an 8 - 10 min period. The respiration rate ($mg\ O_2.L^{-1}.h^{-1}$) was calculated over the linear phase of oxygen consumption for each vessel. The respiration inhibition (%) for FTC test solutions was calculated by comparison of respiration rate with the control.

Findings

Oxygen consumption in the test vessels at 0.1, 1.0, 10, 100 and 1000 $mg.L^{-1}$ of FTC was 14.6, 14.5, 15.0, 15.7 and 15.3 $mg\ O_2.L^{-1}.hr^{-1}$, respectively, compared with mean control values of 15 $mg\ O_2.L^{-1}.hr^{-1}$. Respiratory inhibition for FTC was 2.5, 3.0, 0.0, 0.0 and 0.0% at the increasing concentrations tested, respectively. The no observed effect concentration (NOEC) for FTC was ≥ 1000 $mg.L^{-1}$ and the median effective concentration (EC_{50}) was estimated to be > 1000 $mg.L^{-1}$.

4.2.1.2. Green Freshwater Algae (*Pseudokirchneriella subcapitata*) Test

The toxicity of FTC (Lot No. PP-0053-5044, purity of 99.8%) to green freshwater algae was investigated, following OECD Guideline 201, "Algae, Growth Inhibition Test" (2006) and according to GLPs (TX-162-2002).

Methods

Based on the results of a range finding test, a definitive test was conducted with solutions prepared at the following nominal concentrations 0.32, 1.0, 3.2, 10, 32 and 100 $mg.L^{-1}$ (three replicates each) tested together with an untreated control (six replicates).

The test solutions were prepared in algal growth media by serial dilution of a 100 $mg.L^{-1}$ stock solution. 100 mL aliquots of the prepared test solutions were transferred to test vessels and 0.88 mL of exponentially growing *Pseudokirchneriella subcapitata* culture was inoculated into each flask. The test vessels were incubated on an orbital incubator (100 rpm) within an environmental chamber under continuously illuminated (4,440 to 5,900 lux; 21 to 25 °C) for 72 h. Samples were taken from each test vessel every 24 h for determination of cell concentration using a hemocytometer.

The NOEC and the concentration that resulted in a 10, 20 and 50% reduction in growth rate (E_rC_{10}, E_rC_{20} and E_rC_{50}, respectively) and yield (E_yC_{10}, E_yC_{20} and E_yC_{50}, respectively) were estimated.

Findings

Chemical analysis of test samples taken at 0 and 72 h indicated that FTC was stable over the test period, remaining within ± 20% of nominal concentrations. The mean measured concentrations were 0.34, 1.2, 3.7, 11, 33 and 110 $mg.L^{-1}$ for the 0.32, 1.0, 3.2, 10, 32 and 100 $mg.L^{-1}$ nominal concentrations, respectively.

Daily cell concentrations were used to calculate inhibition compared to the control of average specific growth rates and yield. Statistical analysis using William's test revealed no significant reduction in growth rate or yield in any treatment group compared to the control. Therefore the 72 hour NOEC for growth rate and yield was determined as ≥110 $mg.L^{-1}$. The 0 - 72 hour E_rC_{10}, E_rC_{20}, E_rC_{50} and E_yC_{10}, E_yC_{20}, E_yC_{50} values were estimated to be >110 $mg.L^{-1}$, the highest concentration tested.

4.2.1.3. Invertebrate – Water Flea (*Daphnia magna*)

The toxicity of FTC (Lot No. PP-0053-5044, purity of 99.8%) to the water flea (*Daphnia magna*) was investigated, following OECD Guideline 202, "Daphnia sp., Acute Immobilization Test" (2004) and according to US GLPs (TX-162-2003).

Methods

Daphnia magna were exposed to nominal test concentrations of 6.3, 13, 25, 50 and 100 $mg.L^{-1}$. Daphnids were selected impartially from the culture vessels and placed in each test beaker by adding no more than two daphnids to each beaker until all beakers contained two daphnids. This procedure was repeated until each beaker contained five daphnids. The number of immobilized daphnids in each replicate test vessel was recorded at 24 and 48 hours of exposure. Immobilization was defined as those animals not able to swim within 15 seconds after gentle agitation of the test vessel. Biological observations and observations of the physical characteristics of each replicate test solution were also made and recorded at 0, 24 and 48 hours. The mean measured concentrations tested and the corresponding immobilization data derived from the definitive toxicity test were used to estimate the 24- and 48-hour median effective and no-effect concentrations (EC_{50} and NOEC).

Findings

The mean measured concentrations were 7.2, 14, 29, 54 and 110 $mg.L^{-1}$. Following 48 hours of exposure, no immobilization or adverse effects were observed among daphnids exposed to any treatment level tested (up to a concentration of 110 $mg.L^{-1}$) or the control. The 48-hour EC_{50} value for FTC in Daphnia magna was empirically estimated to be >110 $mg.L^{-1}$, the highest mean measured concentration tested. The NOEC, the highest concentration producing 0% immobilization, was determined to be 110 $mg.L^{-1}$.

4.2.1.4. Fish Acute Toxicity

The effects of FTC (Lot No. PP-0053-5044, purity of 99.8%) on the acute toxicity of fish was investigated with Rainbow Trout (*Oncorhynchus mykiss*), according to OECD Guideline 203, “Fish, Acute Toxicity Test” (1992) and US GLPs (TX-162-2004).

Methods

Rainbow trout were exposed, under static conditions, to nominal FTC concentrations of 6.3, 13, 25, 50 and 100 $mg.L^{-1}$, respectively for 96 hours. The test was initiated when rainbow trout (10 fish per treatment level and the control) were impartially selected and distributed to each aquarium. All aquaria were examined at 0, 24, 48, 72 and 96 hours of exposure as follows: mortalities were recorded and removed, biological observations, including adverse effects (e.g., darkened pigmentation), of the exposed rainbow trout and observations of the physical characteristics of the test solutions (e.g., presence of precipitate, film on the solution's surface) were made and recorded. Effects for this study were based on death, defined as the lack of movement by the exposed organisms (i.e., absence of gill movement and reaction to gentle prodding). The mean measured concentrations tested and the corresponding mortality data derived from the definitive toxicity test were used to estimate the 24-, 48-, 72- and 96-hour median lethal concentrations (LC_{50}) and the NOEC.

Findings

The mean measured concentrations were 7.0, 13, 25, 51 and 110 $mg.L^{-1}$. Following 96 hours of exposure, no adverse effects or mortality were observed among rainbow trout exposed to any treatment level tested (up to a concentration of 110 mg/L^{-1}) or the control. The 96-hour LC_{50} value for FTC on Rainbow Trout was empirically estimated to be >110 $mg.L^{-1}$, the highest mean measured concentration tested. The NOEC was determined to be 110 $mg.L^{-1}$.

4.2.1.5. Acute Aquatic Ecotoxicity Testing and Assessment

FTC was evaluated in acute studies in sewage microorganisms, algae, daphnia, fish, and sewage microorganisms (OECD 209, 201, 202 and 203 respectively). All studies were conducted in accordance with GLP. Data are summarized in the table below.

Table 2. Acute Toxicity Studies in Aquatic Organisms

Study	Result	EC_{50} or LC_{50} / MEEC[1]	Reference
Activated Sludge, Respiration Inhibition Test (OECD 209)	NOEC ≥ 1000 $mg.L^{-1}$ EC_{50} > 1000 $mg.L^{-1}$	885,000	AD-162-2003
Tier 1 - Freshwater Green Algae (OECD 201) *Pseudokirchneriella subcapitata*	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$	97,000	TX-162-2002
Water Fleas (OECD 202) *Daphnia magna*	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$	97,000	TX-162-2003
Rainbow Trout (OECD 203) *Oncorhynchus mykiss*	NOEC ≥ 110 $mg.L^{-1}$ LC_{50} > 110 $mg.L^{-1}$	97,000	TX-162-2004

1 All values approximated to the nearest thousand

The calculated assessment factors in all cases are greater than the required factors (1,000x for Tier 1 and 100x for Tier 2) and in no case were sub-lethal effects observed at concentrations equal to the MEEC. The margin calculations did not factor in the 10-fold dilution typically observed from the POTW to the aquatic system which would increase the margins 10x for algae, water fleas, and fish. These results indicate that FTC release to sewage treatment plants and subsequently to the environment does not pose an environmental risk.

Based on the data above, there is no need to perform Tier 3 Chronic Toxicity testing. However, data was available and thus reported in Section 4.2.2.

4.2.2. Chronic Toxicity (Tier 3)

4.2.2.1. Fish Early Life Stage Test

The effects of FTC (Lot No. PP-0053-5044, purity of 99.8%) on the early life stages of fish was investigated with fathead minnows (*Pimephales promelas)*, according to OECD Guideline 210, “Fish, Early-Life Stage Toxicity Test” (1992) and GLP (TX-162-2005).

Methods

Fathead minnow embryos and fry were exposed, in a flow-through system, for 28 days post-hatch to nominal FTC concentrations of 0.63, 1.3, 2.5, 5.0 and 10 $mg.L^{-1}$, respectively. The experiment (nominal day 0) started with 120 fresh and healthy fertilized fathead minnow eggs per test group, with each test group consisting of two replicate exposure vessels. The fertilized eggs were randomly distributed between twelve egg incubation cups. Each incubation cup contained 60 eggs was suspended in individual exposure aquaria. Test solutions were constantly renewed at a rate of approximately 6.7 aquarium volumes per 24 hours.

Findings

Chemical analysis of test samples taken at Days 0, 1, 5, 12, 19, 26 and 33 indicated that mean measured concentrations of FTC were 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ (between 110-130 % of nominal).

At the completion of hatch (day 5), hatching success in the control averaged 77%. Embryo hatching success in the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels was 80, 78, 70, 78 and 78%, respectively. Kruskal-Wallis' Test determined no significant difference in embryo hatching success among organisms exposed to any treatment level tested as compared to the embryo hatching success of the control organisms. No deformed fry were observed in any treatment level tested or the control.

Following 28 days post-hatch exposure, larval survival in the control averaged 98%. Larval survival in the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels was 95, 98, 95, 98 and 95%, respectively. Williams’ Test determined no significant difference in larval survival in any treatment level tested as compared to the control.

At test termination, total length of larvae exposed to the control averaged 28.6 mm. The mean total length of larvae exposed to the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels was 28.4, 28.2, 28.7, 27.9 and 28.2 mm, respectively. Statistical analysis (Williams' Test) demonstrated no statistically significant reductions in larval length among larvae exposed to any treatment level tested as compared to the control.

Dry weight of larvae in the control averaged 0.0516 g. Dry weight of larvae exposed to the 0.69, 1.5, 3.4, 6.1 and 11 $mg.L^{-1}$ treatment levels averaged 0.0505, 0.0486, 0.0526, 0.0484 and 0.0471 g, respectively. Statistical analysis (Williams’ Test) demonstrated a statistically significant reduction in dry weight among larvae exposed to the 11 $mg.L^{-1}$ treatment level compared to the control.

Based on the overall results of this study, the Lowest-Observed- Effect Concentration (LOEC) in the early life-cycle of fathead minnows was determined to be 11 $mg.L^{-1}$, the highest mean measured concentration tested. The NOEC was determined to be 6.1 $mg.L^{-1}$.

4.2.2.2. Aquatic Invertebrate (*Daphnia magna*) Reproduction Test

The effects of FTC (Lot No. PP-0053-5044, purity of 99.8%) on the reproduction of the aquatic cladoceran *Daphnia magna* were investigated, according to OECD Guideline 211, "Daphnia magna Reproduction Test" (1998) and GLP (TX-162-2006).

Methods

Based on the results of a range-finding test, the definitive test was conducted with the following nominal FTC concentrations, 6.3, 13, 25, 50 and 100 $mg.L^{-1}$. The definitive test was performed using a semi-static design with 10 vessels per test concentration and the untreated control group. Each of the vessels contained one neonate (< 24 h old) *Daphnia magna* in 80 mL test medium.

The test duration was 21 days and the test solutions were renewed 2 - 3 times per week. Test solutions were prepared by serial dilution of a 100 $mg.L^{-1}$ stock solution. The daphnids were fed on a daily basis with a green alga (*Anistrodesmus falcatus*) suspension and a suspension of yeast, cereal leaves and digested flake fish food. During the test, samples of newly prepared test solutions on days 0, 2, 16 and 19 were collected from each treatment group and the control for analytical confirmation of FTC concentration. Additionally, samples of the aged test solutions were collected for analyses on days 2, 5, 19 and 21.

The condition of the parental daphnids and the number offspring produced was monitored daily. The body length of the parental daphnids was measured at the end of the test. Dissolved oxygen, temperature and pH were measured in each test and control solution at the beginning (fresh solutions) and end (aged solutions) of each renewal period.

Findings

Mean measured concentrations of FTC were 7.1, 14, 28, 56 and 110 $mg.L^{-1}$ (110 – 130 % nominal). The FTC concentrations were suitably maintained during the renewal period, the recovery in the aged solutions ranged from 110 – 130% of nominal. The effect parameters were based on the mean measured exposure concentrations.

The first offspring were observed on day 8 at all test concentrations, including the control. The number of immobile adult *D. magna* recorded during the study were 1 (10%) in the control, 28 and 56 $mg.L^{-1}$ test groups, 2 (20%) in the 110 $mg.L^{-1}$ test group and 0 (0)% in the 7.1 and 14 $mg.L^{-1}$ test groups. At the highest FTC dose (110 $mg.L^{-1}$) the mean number of offspring produced per surviving *D. magna* was 155, a reduction of approximately 12% compared to the control. Statistical analysis, using Bonferroni's Test, determined this reduction to be non-significant and therefore the NOEC for reproduction was determined to be $\geq$ 110 $mg.L^{-1}$.

No statistically significant difference (Fisher exact) was detected between the parental survival or mean body length, of any treatment group compared to the control. The 21 day FTC NOEC for each endpoint observed during this study was determined to be $\geq$110 $mg.L^{-1}$.

4.2.2.3. Effects on Larvae of the Midge *Chironomus riparius*

The effects of FTC ([^{14}C]-FTC; batch 645-101-0582, radiochemical purity of 99.6%. FTC; Lot No. 2983-AC-104, purity 99.8%) on the pre-emergent aquatic early life stages of the insect *Chironomus riparius* were investigated, according to OECD Guideline 218, "Sediment Water Chironomid Toxicity Test Using Spiked Sediment" (2004) and GLP (TX-162-2007).

Methods

Following an initial range finding test, a definitive test was conducted with a nominal sediment dry weight concentrations of 1.2, 3.6, 11, 33 and 100 mg.kg^{-1}.

The study was conducted by spiking conditioned artificial sediment (following OECD 218; 1.9% organic carbon, pH 6.6) with appropriate volumes of [^{14}C]-FTC in solvent, so as to give the required nominal concentrations. After ensuring homogeneity, a 1.5 cm layer (123 g wet weight) of the prepared sediments were placed in 600 mL capacity vessels and a 6 cm layer (300 mL) of freshwater carefully delivered over the sediment so as to avoid disturbance of the sediment. The ratio of sediment to water was approximately 1:4 and the total volume of the test system was approximately 375 mL. Four replicate exposure vessels were prepared for each treatment level and controls (untreated and solvent) to monitor the biological results (i.e., percent emergence and development rate) of the exposed midges. Three additional replicate vessels were also prepared for each treatment level and solvent control for analytical measurements to determine exposure concentrations of FTC in the overlying water, pore water and sediment.

After a 2 day equilibration period, ~20 first-instar midge larvae were added to each of the in-life vessels. Midge larvae were provided with food daily and adult emergence recorded up to 28 days post initiation. The endpoints of the test were emergence (%), development time and development rate (1.d^{-1}).

Findings

Results of the sediment sample analysis showed that measured concentrations at preparation were close to nominal (105 -118%). However, concentrations in the aqueous test system were lower, 38 – 67% of nominal on Day 0 and 9.4 – 15% of nominal by test termination on Day 28. The drop in sediment was not reciprocated with concurrent increases in either pore or overlying water concentrations, as such mineralization to $^{14}CO_2$ is the most likely explanation for the lost activity in each test system. The test system will have an initial concentration of active microbes, whose population will have been greatly enhanced by the daily feeding regime with fish food, which may explain the extensive degradation seen.

The first midge emergence in the control was observed on Day 13. Following 28 days of exposure, percent emergence and mean development in the control was 95% and 0.0655, respectively. These results are within the minimum standard criteria established in the OECD guideline, i.e. ≥ 70% emergence and emergence between days 12 and 23. Midge emergence from all the test concentrations was comparable to the controls and statistical analysis, using Dunnett's test determined no significant difference between any treatment level and the controls.

No significant (Dunnett's test) difference in development rate between test groups and the controls was observed. No biological significant effect on emergence rate and development rate was found at the initial measured concentration of 38 $mg.kg^{-1}$, the highest concentration tested. Therefore, the overall NOEC of FTC to *Chironomus riparius* was determined as ≥ 38 $mg.L^{-1}$. Since there was ≤ 50% inhibition of emergence or development rate, the 28-day EC_{50} was estimated to be > 38 $mg.kg^{-1}$ dry weight, based on the initial measured concentration.

Normalized NOEC

As per EMA guidelines {European Medicines Agency (EMEA) 2016} the results from the results from the sediment toxicity tests were recalculated into standard sediment with an organic carbon content of 10%.

$$NOEC_{standard\ sediment} = NOEC_{measured} \times \frac{foc_{standard\ sediment}}{foc_{measured}}$$

Symbol	Parameter	Value (Reference)
Input		
$NOEC_{measured}$	Sediment dweller test NOEC	38 mg kg_{dwt}^{-1}
$foc_{standard\ sediment}$	Fraction of organic carbon standard sediment	0.1 (10%) {European Medicines Agency (EMEA) 2016}
$foc_{measured}$	Fraction of organic carbon test sediment	0.019 (1.9%) (Section 4.2.2.3)
Output		
$NOEC_{standard\ sediment}$	Standard sediment normalized NOEC	200 $mg.kg_{dwt}^{-1}$

4.2.2.4. Tier 3 Assessment

Although not obligated to be performed under the FDA Guidance Document and as part of Gilead's product stewardship efforts, Tier 3 ecotoxicity testing including chronic studies in fish (fathead minnow), water flea, and sediment dweller midge studies were performed.

The concentration in freshly deposited sediment is taken as the PEC for sediment; therefore, the properties of suspended matter are used. The concentration in bulk sediment can be derived from the corresponding water body concentration, assuming a thermodynamic partitioning. The $MEEC_{sediment}$ was calculated following the methodology provided in {European Chemicals Agency 2016, European Medicines Agency (EMEA) 2016} as follows:

$$MEEC_{\text{sediment}} = \frac{K_{susp-water}}{RHO_{susp}} \times MEEC \times CONV_{susp} \times 1000$$

$$K_{susp\text{-}water} = Fwater_{susp} + Fsolid_{susp} \times Kp_{susp} / 1000 \times RHO_{solid}$$

$$CONV_{susp} = \frac{RHO_{susp}}{Fsolid_{susp} \times RHO_{solid}}$$

$$Kp_{susp} = Foc_{susp} \times Koc$$

Symbol	Parameter	Value (Reference)
Input		
MEEC	Maximum expected environmental Concentration (in the water)	1.13 µg.L^{-1} (Section 4.1.4)
$Fwater_{susp}$	Fraction water in suspended matter	0.9 m^3.m^{-3} {European Chemicals Agency 2016}
$Fsolid_{susp}$	Fraction solids in suspended matter	0.1 m^3.m^{-3} {European Chemicals Agency 2016}
RHO_{solid}	Bulk density of solids	2500 kg m^{-3} {European Chemicals Agency 2016}
Foc_{susp}	Weight fraction organic carbon in suspended matter	0.1 kg kg^{-1} {European Chemicals Agency 2016}
K_{oc}	Organic carbon normalised partition coefficient	45.6 dm^3 kg^{-1} (worst-case see Section 4.1.2)
RHO_{susp}	Bulk density of suspended matter	1150 kg m^{-3} {European Chemicals Agency 2016}
1000	Conversion factor	1000 dm^3.m^{-3} {European Chemicals Agency 2016}
Intermediate Results		
$K_{susp\text{-}water}$	Sediment matter water partition coefficient (v/v)	2.04 m^3 m^{-3}
Kp_{susp}	Partition coefficient solids and water in suspended matter (v/w)	4.56 L.kg^{-1}
$CONV_{susp}$	Conversion factor for sediment concentrations: wwt to dwt	4.6 kg$_{wwt}$.kg$_{dwt}$$^{-1}$
Output		
$MEEC_{sediment}$	Predicted Environmental Concentration in sediment	9.2 µg kg$_{dwt}$$^{-1}$ 2.0 µg.kg$_{wwt}$$^{-1}$

All studies were conducted in accordance with GLPs. Data are summarized in the Table 3. Based on these data, (though not obligated to be performed under the FDA Guidance Document), a Tier 3 Assessment was performed. The Test Tier 3 Assessment compares the lowest EC_{50} or LOEC of chronic or reproductive studies to the MEEC. As per the FDA Guidance Document, if the ratio is ≥ 10 and there are no effects at the MEEC, no environmental impact is anticipated. Since the NOEC ranged from 5,000 – 97,000 greater than the MEEC for three different organisms, no environmental impact is anticipated. The margin calculations did not factor in the 10-fold dilution typically observed from the POTW to the aquatic system which would increase the margins 10-fold.

Table 3. Tier 3 Chronic and Reproductive Toxicity Studies

Study	Results	NOEC / MEEC[1]	Reference
Fathead Minnow (OECD 210) *Pimephales promelas* Fish Early Life Cycle	LOEC = 11 $mg.L^{-1}$ NOEC = 6.1 $mg.L^{-1}$	5,000	TX-162-2005
Water Fleas (OECD 211) *Daphnia magna* Reproduction	NOEC ≥ 110 $mg.L^{-1}$ LOEC > 110 $mg.L^{-1}$	97,000	TX-162-2006
Sediment Dwellers (OECD 218) Chironomid Larvae Toxicity	NOEC ≥ 200 $mg.kg_{dwt}^{-1}$ LOEC > 200 mg kg_{dwt}^{-1}	22,000	TX-162-2007

1. All values approximated to the nearest thousand. $MEEC_{sediment}$ values used for the Chironomid (OECD 218) study

4.3. Summary

A standard battery of environmental fate and effects studies has been conducted to evaluate the environmental risk associated with the use of FTC. FTC is likely to partition mostly into water and sediment and not bioaccumulate in the environment.

A battery of acute, chronic and reproductive effects studies were conducted in aquatic organisms and sediment dwellers. The results of these studies showed low toxicity. The results of these studies were compared to the MEEC. The EC_{50} and LC_{50} concentration / MEEC ratios at all three tiers of assessment based on one (1) acute study (Tier 1), a battery of acute studies (Tier 2), and chronic studies (Tier 3) were greater than their required assessment factors (1000x for Tier 1, 100x for Tier 2, and 10x for Tier 3) and there were no effects observed at the corresponding MEEC. Based on the above data and risk assessment conclusions, the current data indicates that FTC is of low risk to the environment based on current use patterns. Gilead therefore requests approval for the anticipated use based on no environmental impact of this clinical use.

5. MITIGATION MEASURES

Based on the evidence presented, no environmental mitigation measures are needed.

6. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action and therefore no alternatives are proposed.

7. LIST OF PREPARERS

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Education

Indiana University School of Informatics Indianapolis, IN	PhD	Health Informatics (Focus in Toxicology)	2010
University of Texas School of Public Heath Houston, TX	MPH	Toxicology	2001
Texas A&M University College Station, TX	BS	Biomedical Sciences	1998

Job History

Gilead Sciences Drug Safety Evaluation 333 Lakeside Drive Foster City, Ca 94404	Director	2015-present

- Lead of the Environmental and Occupational Toxicology group
- Manage Environmental Risk Assessments (ERAs) for Gilead compounds, including the environmental toxicity and fate studies
- Oversee derivation of Occupational Exposure Limits (OELs) for worker safety
- Oversee derivation of Permissible Daily Exposures (PDEs) for pharmaceutical cleaning validation
- Oversee GHS classification and Safety Data Sheet language development
- Manage the assessment of impurities, including QSAR assessment of mutagenic impurities, PDEs for reagents, solvents and metals, extractables and leachables, and qualification toxicity testing
- Manage occupational health hazard testing of Gilead compounds

Amgen Product Stewardship One Amgen Center Drive Thousand Oaks, Ca	EHS Sr. Manager	2010-2015

- Lead of the Product Stewardship group which provided toxicology assessments for product and occupational safety, hazard information on Safety Data Sheets, ERAs, and risk assessments for non-conformance investigations
- Chair of the Hazard Evaluation Committee which decides safe exposure levels to pharmaceuticals (occupational and product safety), and hazardous chemicals
- Global industry leader in risk assessment for emerging issues and regulatory guidance documents

Lilly Research Laboratories	Consultant Toxicologist	2008-2010
Eli Lilly and Company	Assistant Sr. Toxicologist	2004-2008
Indianapolis, IN	Toxicologist	2000-2004
Risk Assessment Group		

- Risk assessment leader for chemistry and quality to ensure the manufacture of pharmaceuticals are safe from potential residual levels of hazardous chemicals such as mutagens, carcinogens, or reproductive toxicants

Lyondell Chemical Company Houston, TX	Toxicologist	1999-2001
University of Texas Houston School of Public Health Houston, TX	Graduate Research Assistant	1998-2001
Moffitt Cancer Center	Research Assistant	1997

Certifications / Expertise

Diplomat of the American Board of Toxicology
Environmental and Occupational Toxicology
Benchmark Dose Modeling
Computer Modeling / Informatics
Threshold of Toxicological Concern
Toastmasters – Competent Communicator

Professional Associations

Society of Toxicology 1999 – present

- Occupational Health Specialty Section (Served as President and Vice President)
- Risk Assessment Specialty Section

PhRMA LDKIT (Chair of Risk Assessment Subgroup) 2010 – 2015

- Led the development of ICH M7 (i.e., mutagenic impurities) and its corresponding addendum

ILSI HESI Workgroups 2009 – 2011

- Short-Term / Intermittent Exposure to Carcinogens
- Risk Assessment of Multiple Carcinogens
- Threshold of Toxicological Concern

Publications

Bercu JP, Morinello E, Sehner C, Shipp BK, Weideman PA. 2016. Point of departure (PoD) selection for the derivation of Acceptable Daily Exposures (ADEs) for active pharmaceutical ingredients (APIs). Regul Toxicol Pharmacol. 2016. doi: 79 Suppl 1:S48-56.

Hayes EP, Jolly RA, Faria E, Barle EL, Bercu J, Molnar L, Naumann B, Olson M, Pecquet A, Sandhu R, Shipp BK, Sussman R, Weideman P. 2016. A harmonization effort for acceptable daily exposure application to pharmaceutical manufacturing - Operational considerations. Regul Toxicol Pharmacol. 79 Suppl 1:S39-47.

Faria EC, Bercu JP, Dolan DG, Morinello EJ, Pecquet AM, Seaman C, Sehner C, Weideman PA. 2016. Using default methodologies to derive an acceptable daily exposure (ADE). Regul Toxicol Pharmacol. 2016. 79 Suppl 1:S28-38.

Amberg A, Beilke L, Bercu J, Bower D, Brigo A, Cross KP, Custer L, Dobo K, Dowdy E, Ford KA, Glowienke S, van Gompel J, Harvey J, Hasselgren C, Honma M, Jolly R, Kemper R, Kenyon M, Kruhlak N, Leavitt P, Miller S, Muster W, Nicolette J, Plaper A, Powley M, Quigley DP, Reddy MV, Spirkl HP, Stavitskaya L, Teasdale A, Weiner S, Welch DS, White A, Wichard J, Myatt GJ. 2016. Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses. Regul Toxicol Pharmacol. 77:13-24.

Weideman, P, Bercu JP, Callis C, Dolan DG, Faria E, Flueckiger A, Gould J. Hayes EP, Jolly R, Barle EL, Luo W, Molnar LR, Morinello E, Naumann BD, Olson M, Pfister T, Sandhu R, Sargent, EV, Seaman C. 2015. Deriving health-based exposure limits in the pharmaceutical industry. Contract Pharma. 17(7):74.

Stanard B, Dolan DG, Hanneman W, Legare M, Bercu JP. 2015. Threshold of toxicological concern (TTC) for developmental and reproductive toxicity of anticancer compounds. Regul Toxicol Pharmacol. 72(3):602-9.

Pfister T, Dolan D, Bercu J, Gould J, Wang B, Bechter R, Barle EL, Pfannkuch F, Flueckiger A. 2014. Bioavailability of Therapeutic Proteins by Inhalation—Worker Safety Aspects. Ann. Occup. Hyg. 58(7):899-911.

Galloway SM, M. Reddy MV, McGettigan K, Gealy R, Bercu JP. 2013. Potentially mutagenic impurities: Analysis of structural classes and carcinogenic potencies of chemical intermediates in pharmaceutical syntheses supports alternative methods to the default TTC for calculating safe levels of impurities. Regul. Toxicol. Pharmacol. 66(3):326-35.

Bercu JP, Sharnez R, Dolan DG. 2013. Advancing Toxicology in RiskMAPP: Setting ADEs Based on the Subsequent Drug Substance. Regul. Toxicol. Pharmacol. 65(1):157-61.

Bercu JP, Dolan DG. 2013. Application of the threshold of toxicological concern concept when applied to pharmaceutical manufacturing operations intended for short-term clinical trials. Regul. Toxicol. Pharmacol. 65(1):162-7.

Sharnez R, Aisenbrey E, Bercu J, Binkley D, Tholudur A. 2012. Cleaning validation of multiproduct equipment— Acceptance limits for inactivated product. Part II—Application of the comparable quality approach to intrasite assessments. J. Validation Technol. 18(2):17-25.

Felter SP, Conolly RB, Bercu JP, Bolger PM, Boobis AR, Bos PMJ, Carthew P, Doerrer NG, Goodman JI, Harrouk WA, Kirkland DJ, Lau SS, Llewellyn GC, Preston RJ, Schoeny R, Schnatter AR, Tritscher A, van Velsen F, Williams GM. 2011. A Proposed Framework for Assessing Risk from Less-Than-Lifetime Exposures to Carcinogens. Crit. Rev. Toxicol. 41(6):507-44.

Bercu JP, Jolly RA, Flagella KM, Baker TK, Romero P, Stevens JL. 2010. Toxicogenomics and cancer risk assessment: A framework for key event analysis and dose-response assessment for nongenotoxic carcinogens. Regul. Toxicol. Pharmacol 58(3):369-81.

Bercu JP, Morton SM, Deahl JT, Gombar VK, Callis CM, van Lier RBL. 2010. *In silico* approaches to predicting cancer potency for risk assessment of genotoxic impurities in drug substances. Regul. Toxicol. Pharmacol. 57(2-3):300-6.

Raillard SP, Bercu JP, Riley CM, Baertschi SW. 2010. Prediction of drug degradation pathways leading to potential genotoxic impurities. Org. Proc. Res. Dev. 14(4): 1015-1020.

Baertschi SW, De Antonis D, McKeown A, Bercu JP, Raillard S, Riley CM. 2010. Stress testing as a predictive tool for the assessment of potential genotoxic degradants. In: Pharmaceutical Stress Testing: Predicting Drug Degradation, 2nd Ed. (Editors: S.W. Baertschi SW, Alsante KM, and Reed RA). Informa Life Sciences.

Callis CM, Bercu JP, DeVries KM, Dow LK, Robbins DK, Varie DL. 2010. Risk assessment of genotoxic impurities in marketed compounds administered over a short-term duration: Applications to oncology products and implications for impurity control limits. Org. Proc. Res. Dev. 14(4): 986-992.

Bercu JP, Dobo KL, Gocke E, McGovern T. 2009. Summary of Symposium: Overview of genotoxic impurities in pharmaceutical development. Int. J. Toxicol. 28(6): 468-78.

Bercu JP, Callis CM. 2009. Comprehensive toxicology risk assessment for genotoxic impurities. Org. Proc. Res. Dev. 13(5): 938.

Dobo KL, Obach RS, Luffer-Atlas D, Bercu JP. 2009. A strategy for risk assessment for human genotoxic metabolites. Chem. Res. Toxicol. 22(2): 348-56.

Bercu JP, Hoffman WP, Lee C, Ness DK. 2008. Quantitative assessment of cumulative carcinogenic risk for multiple genotoxic impurities in a new drug substance. Regul. Toxicol. Pharmacol. 51(3): 270-7.

Bercu JP, Parke NJ, Fiori JM, Meyerhoff RD. 2008. Human health risk assessments for three neuropharmaceutical compounds in surface waters. Regul. Toxicol. Pharmacol. 50(3): 420-7.

Bercu JP. 2001. Compounds that bind to the gamma-aminobutyric acid benzodiazepine ionophore complex modulate the cellular response to oxidant stress. University of Texas Health Science Center at Houston. School of Public Health.

Abstracts/Invited Presentations

Bercu JP. 2016. Incorporating (Q)SAR and Expert Reviews to Ensure Compliance with ICH M7. QSAR Conference.

Bercu JP. 2016. Practical Implementation of (Q)SAR and Expert Review for Compliance with ICH M7 Guidelines. Streamlining Drug Discovery and Development.

Bercu JP. 2016. Impurities: The Good, the Bad, and the Ugly. American College of Toxicology Webinar.

Bercu JP. 2015. Generating AI's and PDE's for Mutagens and Carcinogens per the ICH M7 Guideline. American Association of Pharmaceutical Scientists (AAPS).

Bercu JP. 2015. How OELs and ADEs Develop over the Life Cycle of a Drug. Highly Potent API (HPAPI) Summit.

B. Stanard B, Bercu JP, Hanneman W, Legare ME. 2015. Threshold of Toxicological Concern (TTC) for Anticancer Compounds. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract #201.

Bercu JP, Gombar, VK. 2014. In Silico Methods for Mutagenicity Prediction vis a vis ICH M7 Guidance. Session Chair. American College of Toxicology.

Bercu JP. 2013. Addressing Risks of the Potential Presence of Multiple Genotoxic/Carcinogenic Impurities in Pharmaceuticals. Society of Toxicology.

Bercu JP. 2010. Evaluating Genotoxicity SAR: Experience from Analysis of Pharmaceutical Impurities. Environmental Mutagen Society, Annual Meeting.

Bercu JP, Morton SM, Deahl JT, Gombar VK, Callis CM, Zwickl CM, van Lier RL. 2009. Risk assessment of genotoxic impurities in a pharmaceutical using in silico tools. Toxicology and Risk Assessment Conference.

Bercu JP. 2009. Managing Genotoxic Impurities throughout Development of Pharmaceutical: Control Strategies and Case Studies. Genetic Toxicology Association.

Bercu JP. 2009. Short-Term and Intermittent Exposure to Carcinogens - Current Approaches. Workshop Sponsored by International Life Sciences Institute - Health Environmental and Sciences Institute.

Bercu JP. 2009. The Threshold of Toxicological Concern - Background and Applications. Session Chair. American College of Toxicology.

Hoffman WP, Ness D, Lee C, Bercu JP. 2009. Linking CMC and Toxicology: The Use of Cumulative Carcinogenic Risk for Multiple Genotoxic Impurities Criteria. Midwest Biopharmacueticals Statistics Workshop.

Bercu JP. 2008. Risk assessment of genotoxic and carcinogenic impurities: Current issues and case studies. Int. J. Toxicol. 27(6): 405.

Bercu JP. 2008. Risk Assessment of Genotoxic and Carcinogenic Impurities: Current Issues and Case Studies. American College of Toxicology.

Bercu JP. 2008. Using Genetic Toxicology Information to Evaluate Safety of Impurities and Metabolites for Pharmaceuticals. Society of Toxicology; National Meeting.

Bercu JP. 2008. Risk Management of Genotoxic Compounds in the Manufacture of Pharmaceuticals. Toxicology and Risk Assessment Conference.

Bercu JP, Dobo KL. 2007. Identification and risk assessment of human genotoxic drug metabolites. The Toxicologist. 96(1): 331.

Callis CM, Bercu JP, Moreno MA. 2007. Toxicology and analytical chemistry: An integrated strategy for leachable studies on a polymeric stopper material. Parenteral Drug Association.

Bercu JP, Callis CM, Fiori JM, Meyerhoff RD. 2006. Process to minimize genotoxic impurities in production of a new drug substance. The Toxicologist. 90(1): 179.

Bercu JP, Fiori JM, Meyerhoff RD. 2004. Human health risk assessment for environmental residues of atomoxetine. The Toxicologist. 78(1-S): 152.

Callis CM, Fiori JM, Bercu JP, Meyerhoff RD. 2004. The Threshold of Toxicological Concern (TTC) as an acceptable limit for leachables from polymeric materials into pharmaceutical ingredients. Parenteral Drug Association.

Bercu JP, Smith MA. 2000. Modulation of the benzodiazepine (BZD) receptor/GABA complex affects cell death induced by oxidant stress in Madin Darby canine kidney (MDCK) cells. The Toxicologist. 54(1): 406.

Bercu JP. Gulf Coast Society of Toxicology Meeting. 1999. Modulation of Benzodiazepine (BZD) Receptor/ GABAA Complex Affects Cell Death Induced by Oxidant and Stress in Madin Darbin Kidney (MDCK) Cells.

8. REFERENCES

The following references were used in the preparation of this Environmental Assessment and are generally available. Specific citations from these references may be obtained upon request.

European Chemicals Agency. Guidance on information requirements and Chemical Safety Assessment. Chapter R.16: Environmental exposure assessment 3.0. Helsinki, Finland. February, 2016.

European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP). Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'. [EMA/CHMP/SWP/44609/2010 Rev. 1]. London, England. May, 2016.

Food & Drug Administration (FDA). CFR-Code of Federal Regulations Title 21 [21CFR25.31]. Revised 21 September. 2016.

U. S. Department of Health and Human Services (DHHS), Food & Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologic Evaluation and Research (CBER). Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications. CMC 6. Revision 1. July. 1998.

9. APPENDICES

Appendix 1. Emtricitabine Data Summary Table
Appendix 2. Referenced Study Reports

9.1. Nonconfidential Appendices

Appendix 1. Emtricitabine Data Summary Table

Emtricitabine Data Summary Table	
Physical/Chemical Characterization	
Water Solubility	112 mg/mL
Dissociation Constants	2.65
Octanol/Water partition Coefficient (Log K_{ow}) (OECD 107)	-0.693 (pH 4) -0.670 (pH 7) -0.693 (pH 10)
Vapor Pressure	Presumably non-volatile
Sorption/Desorption (K_{oc}) (OECD 106)	21.1 – 45.6
Depletion Mechanisms	
Hydrolysis	No data available
Aerobic Biodegradation in Water (OECD 301D)	Not readily biodegradable
Photolysis	Absorbs in the UV range, but assumed not to be photolabile
Metabolism	FTC is minimally transformed (13%), most appears unchanged in urine (86%)
Environmental Effects	
Microbial Inhibition **Activated Sludge (OECD 209)**	NOEC ≥ 1000 $mg.L^{-1}$ EC_{50} > 1000 $mg.L^{-1}$
Acute Toxicity Freshwater Green Alga (OECD 201) *Pseudokirchneriella subcapitata*	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$
Water Fleas (OECD 202) *Daphnia magna* Acute Toxicity	NOEC ≥ 110 $mg.L^{-1}$ EC_{50} > 110 $mg.L^{-1}$
Rainbow Trout (OECD 203) *Oncorhynchus mykiss*	NOEC ≥ 110 $mg.L^{-1}$ LC_{50} > 110 $mg.L^{-1}$
Chronic Toxicity Fathead Minnow (OECD 210) *Pimephales promelas* Fish Early Life Cycle	LOEC = 11 $mg.L^{-1}$ NOEC = 6.1 $mg.L^{-1}$
Water Fleas (OECD 211) *Daphnia magna* Reproduction	NOEC ≥ 110 $mg.L^{-1}$ LOEC > 110 $mg.L^{-1}$
Sediment Dwellers (OECD 218) Chironomid Larvae Toxicity	Normalized NOEC ≥ 200 $mg.kg_{dwt}^{-1}$ Normalized LOEC > 200 $mg.kg_{dwt}^{-1}$

9.2. Confidential Appendices

Appendix 2. Referenced Study Reports

This section provides a list of all study reports that have been cited in the present Environmental Assessment and can be accessed via the hyperlinks below.

Cross-reference to Gilead Nonclinical Reports

Study Report Number	Study Title
BA-162-2001	Validation of the Analytical Method for the Determination of Radiolabelled Emtricitabine in Sediment
AD-162-2001	Emtricitabine - Determining the Adsorption Coefficient (Koc) Following OECD Guideline 106
AD-162-2002	Determining the Partitioning Coefficient (n-Octanol/Water) of Emtricitabine by the Flask-shaking Method Following OECD Guideline 107
AD-162-2003	Activated Sludge Respiration Inhibition Test to Emtricitabine Following OECD Guideline 209
AD-162-2004	Emtricitabine – Aerobic and Anaerobic Transformation in Aquatic Sediments Systems Following OECD Guideline 308
1784	Emtricitabine (CAS # 143491-57-0): Ready Biodegradability Evaluation (OECD 301D)
TX-162-2002	Acute Toxicity of Emtricitabine to the Freshwater Green Alga *Pseudokirchneriella subcapitata* Following OECD Guideline #201
TX-162-2003	Acute Toxicity of Emtricitabine to Water Fleas, *Daphnia magna* Under Static Conditions, Following OECD Guideline #202
TX-162-2004	Acute Toxicity of Emtricitabine to Rainbow Trout (*Oncorhynchus mykiss)* Under Static Conditions, Following OECD Guideline #203
TX-162-2005	Early Life-Stage Toxicity Test of Emtricitabine with Fathead Minnow, (*Pimephales promelas*), Following OECD Guideline #210
TX-162-2007	Emtricitabine; Toxicity test with Sediment-Dwelling Midges (Chironomus riparius) Under Static Conditions, Following OECD Guideline 218
TX-162-2006	Emtricitabine – Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Static Renewal Conditions, Following OECD Guideline #211

James Laurenson

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Michael Furness

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LABELING

IQA Review Guide Reference

NDA 210251

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BIKTARVY safely and effectively. See full prescribing information for BIKTARVY.

BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: XXXX

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets
Dosage form, route of administration	tablets, for oral use
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use To replace with the following BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, 50 mg/200 mg/25 mg, for oral use

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with BIKTARVY
Prior to or when initiating BIKTARVY, test patients for hepatitis B virus infection [see Warnings and Precautions (5.1)].

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus [see Warnings and Precautions (5.4)].

2.2 Recommended Dosage
BIKTARVY is a three-drug fixed dose combination product containing 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)].

2.3 Not Recommended in Patients with Severe Renal Impairment
BIKTARVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute [see Use in Specific Populations (8.6)].

2.4 Not Recommended in Patients with Severe Hepatic Impairment
BIKTARVY is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) [see Use in Specific Popoulations (8.7) and Clinical Pharmacology (12.3)].

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food [see Clinical Pharmacology (12.3)].

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS
Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). The tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).
Strengths: in metric system	contains 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).
Active moiety expression of strength with equivalence statement (if applicable)	50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The tablets are purplish brown, capsule-shaped, film-coated, and debossed with "GSI" on one side and "9883" on the other side.

4. *Section 11 Description*

11 DESCRIPTION

BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

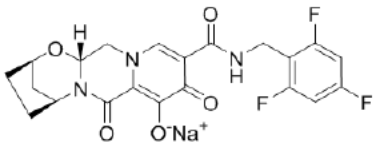
- BIC is an integrase strand transfer inhibitor (INSTI)
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′ - monophosphate.

Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 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 iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Bictegravir: The chemical name of bictegravir sodium is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), (2R,5S,13aR)-.

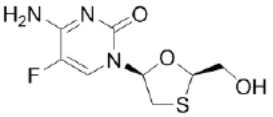
Bictegravir sodium has a molecular formula of $C_{21}H_{17}F_3N_3NaO_5$ and a molecular weight of 471.4 and has the following structural formula:



Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

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

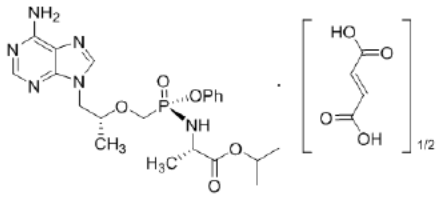
FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.2 and has the following structural formula:



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)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a formula weight of 534.5 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
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide)
Dosage form and route of administration	a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 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 iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	BIC is an integrase strand transfer inhibitor (INSTI) FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI). TAF, an HIV NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.
Chemical name, structural formula, molecular weight	Available
If radioactive, statement of important nuclear characteristics.	NA

Other important chemical or physical properties (such as pKa or pH)	Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C. FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C. 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.

5. *Section 16 How Supplied/Storage and Handling*

HOW SUPPLIED/STORAGE AND HANDLING
BIKTARVY tablets are purplish brown, capsule-shaped, and film-coated with "GSI" debossed on one side and "9883" on the other side. Each bottle contains 30 tablets (NDC 61958-2501-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) [redacted] (b) (4) 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) [redacted] (b) (4) .

Store below 30 °C (86 °F).

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

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Each BIKTARVY tablet contains 50 mg of bictegravir (BIC) [redacted] (b) (4) 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) [redacted] (b) (4)
Available units (e.g., bottles of 100 tablets)	Each bottle contains 30 tablets (NDC 61958-2501-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	BIKTARVY tablets are purplish brown, capsule-shaped, and film-coated with "GSI" debossed on one side and "9883" on the other side.
Special handling (e.g., protect from light)	•Keep container tightly closed. •Dispense only in original container.
Storage conditions	Store below 30 °C (86 °F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	To add Manufacturer/distributor name (21 CFR 201.1(h)(5))

Reviewer's Assessment of Package Insert: ***{Adequate/Inadequate}***

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

[redacted]

2.

Carton Label

(b) (4)

[redacted]

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tradename™ (bictegravir, emtricitabine, tenofovir alafenamide) tablets 50 mg/200 mg/25 mg Acceptable to prominence, font size, and prominence	(b) (4)
Dosage strength	50 mg/200 mg/25 mg And Each tablet contains 50 mg of bictegravir (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide (equivalent to 28 mg of tenofovir alafenamide fumarate).	
Net contents	30 tablets	
"Rx only" displayed prominently on the main panel	Rx only	
NDC number (21 CFR 207.35(b)(3)(i))	NDC 61958-2501-1	
Lot number and expiration date (21 CFR 201.17)	The space is available. However, it is not indicated if the space is reserved for lot number and expiration date.	
Storage conditions	Store below 30 °C (86 °F) Keep container tightly closed. Dispense only in original container. See package insert for dosage and administration. KEEP OUT OF THE REACH OF CHILDREN	
Bar code (21CFR 201.25)	Available	
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc. Foster City, CA 94404	

	Made in Germany	(b) (4)
And others, if space is available		

Reviewer's Assessment of Labels: ***{Adequate/Inadequate}***

Per 21 CFR 201.17, confirm if the space is available for lot number and expiration date in the proposed container label.

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies:

In highlights of prescribing information, "BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use" should be replaced with "BIKTARVY™ (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, 50 mg/200 mg/25 mg, for oral use."

In Section 16 How Supplied/Storage and Handling, please add names for manufacturer/distributor per 21 CFR 201.1(h)(5).

Per 21 CFR 201.17, confirm if the space is available for lot number and expiration date in the proposed container label.

Overall Assessment and Recommendation:

It is recommended for approval upon the competition of the above changes from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Yong Wang

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

Yong Wang

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Balajee Shanmugam

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BIOPHARMACEUTICS

Product Background:

NDA: 210251
Submission Type: 505(b)(1) NDA; using a Tropical Disease Voucher (Priority)
Chemical Type: Type 1 NME (for bictegravir), Type 4 New Combination

Drug Product Name / Strength: Bictegravir/Emtricitabine/Tenofovir Alafenamide, (B/F/TAF), 50 mg (as bictegravir free base)/ 200 mg/ 25 mg, Immediate-Release (b) (4) Fixed Dose Combination Tablet

Route of Administration: Oral
Recommended Dosage (for treatment of HIV infection in adults): One tablet once daily with or without food

Applicant Name: Gilead Sciences, Inc.

Review Recommendation:
From the Biopharmaceutics perspective, NDA 210251 for B/F/TAF (50 mg/200 mg/25 mg) Tablets is recommended for APPROVAL.

Review Summary:
The proposed QC dissolution method and the revised dissolution acceptance criteria as tabulated below are approved for the routine QC testing of the B/F/TAF (50 mg/200 mg/25 mg) Tablets (submitted under NDA 210251).

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddle)	75 rpm	pH 5.5 (50 mM) citrate buffer, 37 ± 0.5°C	900 mL	For all three APIs: Q = (b) (4)% at 30 min

The proposed to-be-marketed drug product has the same formulation, appearance, and drug product manufacturing process/site, and API suppliers as the Phase 3 clinical/primary stability batches. The proposal to add an alternate drug product manufacturer for commercialization was supported with evidence of comparable *in vitro* dissolution profiles between the test and the reference drug products. Similarly, adequate *in vivo* PK and *in vitro* dissolution profile data are available to support the slight change in formulation of the B/F/TAF (50 mg/ 200 mg /25 mg) Tablets used in clinical development studies.

List Submissions being reviewed:
SDN-2, 6/12/2017 (Original NDA)
SDN-9, 8/3/2017 (Response to Quality Information Request – dissolution)
SDN-10, 8/22/2017 (Response to Quality Information Request - particle size)
SDN-14, 9/28/2017 (Response to Quality Information Request – dissolution)

Concise Description Outstanding Issues Remaining:
None

BCS Designation

Bictegravir (BIC, formerly known as GS-9883-01) is a New Molecular Entity (NME) whereas Emtricitabine (FTC) and Tenofovir Alefamide (TAF) are APIs of approved FDA antiviral drug products.
The Applicant considers the drug substance BIC as exhibiting the characteristics of a BCS-2 (low solubility/high permeability) drug substance. Additionally, the Applicant considers FTC as a BCS-1 (high solubility/high permeability) drug substance, and TAF as a BCS-3 (high solubility/low permeability) drug substance.

Reviewer's Assessment:

Solubility: *Low Solubility for BIC, High Solubility for both FTC and TAF*
BIC exhibits low solubility (per BCS criteria), and pH-independent solubility in media without surfactant. On the other hand, per BCS criteria, both FTC and TAF are highly soluble because < 250 mL volumes of various pH media are anticipated to be sufficient to dissolve the individual labeled amounts of FTC and TAF at 37 °C. When tested individually, the solubility values of BIC, FTC, and TAF in media with pH across the physiologic range were at least 0.1 mg/mL, 100 mg/mL, and 4.7 mg/mL, respectively, at room temperature (~ 20-25 °C). Note that for the treatment of HIV infection in adults, the proposed dosage of the B/F/TAF (50/200/25 mg) Tablet is one tablet orally once daily with or without food.

Permeability: *Low Permeability for BIC and TAF; High Permeability for FTC*
The Clinical Pharmacology Reviewer (Dr. Vikram Arya) confirmed that at least 59% of the administered dose of bictegravir is absorbed, i.e., following administration of an oral dose of 100-mg [^{14}C] BIC under fed conditions, with a 91% recovery rate. The absolute bioavailability of BIC is not known, and so based on the results of the human ADME Study, the permeability of BIC is deemed to be *Low*. Of note, the Applicant states that based on the results of a Caco-2 permeability study, BIC exhibits high permeability with concentration dependent efflux; the efflux ratios were 4.4 and 1.5 at BIC concentrations of 10 µM and 88 µM (solubility limit), respectively. Refer to the Clinical Pharmacology and Pharmacology/Toxicology Reviews for the evaluation of the Caco-2 permeability study results.

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(b) (4)

Dissolution Acceptance Criteria *- REVISED ACCEPTANCE CRITERIA ACCEPTABLE*

For the routine QC testing of the B/F/TAF (b) (4) tablets, the proposed QC dissolution acceptance criteria are "Meet the USP and Ph. Eur. criteria for the amounts of BIC, FTC, and TAF dissolved at 30 minutes when Q is (b) (4)%." Per the Applicant, the proposed dissolution acceptance criterion takes into consideration (1) the immediate-release dosage form of the to-be-marketed drug product, (2) the need to ensure complete disintegration and dissolution within the typical gastric emptying time, (3) the plasma Tmax of the three API's, i.e., 0.5 to 2 hours, and (4) the capability to discriminate between clinically acceptable drug product batches and aberrant tablets.

This Reviewer recommends tightening of the dissolution acceptance criterion to 'Q = (b) (4)% at 30 min' for all three APIs, based on (1) the *in vitro* dissolution profiles of the three APIs provided for the Phase 3 clinical trial batches which all converged at the 30 minute time point, and (2) considering that this revised dissolution acceptance criterion (Q = (b) (4)% at 30 min for all 3 APIs) is sufficient to reject the aberrant drug product batch as shown in Figures 1 and 2 above. Note that an earlier specification time point (i.e., 15 or 20 min) was not chosen by this Reviewer to avoid/minimize the potential for rejecting B/F/TAF tablet batches with *in vitro* dissolution profiles similar to Phase 3 clinical trial Batches EN1609B and EN1610B. (b) (4)

For the six drug product batches undergoing stability testing, the reported mean dissolution data at 30 min for all three APIs ranged from 95 – 104%, indicating conformance to this Reviewer's recommended dissolution acceptance criterion of 'Q = (b) (4)% at 30 min' over up to 12 months of long-term storage (25°C/60%RH and 30°C/75%RH). Note that the corresponding range of mean dissolution for all three APIs at 30 min was 94% - 103% after storage at 40°C/75%RH for up to 6 months for the same stability batches.

In the 9/18/2017 response to the Biopharmaceutics Information Request dated 9/14/2017, the Applicant agreed to revise the QC dissolution acceptance criterion to 'Q = (b) (4)% in 30 min for all three APIs', and the pertinent NDA documents were updated accordingly.

Bridging of Formulations

Reviewer's Assessment: *ADEQUATE*

The pivotal Phase 3 clinical trials GS-US-380 -1489, -1490, -1844, and -1878 used two (i.e., original and final) formulations of the B/F/TAF [50/200/25 mg] FDC (b) (4) tablets. Additionally, the original formulation was used in the Relative BA and Food-Effect Study GS-US-141-1233, and various drug-drug interaction studies (GS-US-380 -1999, -3908, -3909, and -4270). Note that the original formulation is different from the final formulation only in terms of the (b) (4) Both *in vivo* PK and *in vitro* dissolution profile data are available to bridge the final formulation to the original formulation used in these pivotal Phase 3 and Phase 1 clinical studies. Based on the population PK analysis conducted by the Pharmacometrics Reviewer (Dr. Ada Zhuang), it was confirmed that "formulation" was not a significant covariate of BIC pharmacokinetics. Likewise, the Applicant's own Population PK analysis did not find "formulation" to be a significant covariate of TAF pharmacokinetics. Additionally, the original formulation batches (EN1503B and EN1504B) exhibited very rapid dissolution profiles in the proposed QC medium, similar to the final formulation (pilot scale) batches used in the Phase 3 clinical trials.

The to-be-marketed drug product and the final formulation used in the Phase 3 clinical trial and the registration drug product batches have the same appearance, formulation, and manufacturing process. The drug product manufacturing site is also the same for the designated commercial formulation and the final formulation used in the Phase 3 clinical trial, however; the Applicant has proposed to add an alternate drug product manufacturing site. Using the proposed QC dissolution method, it was observed that the pilot-scale and process scale-up batches produced by (b) (4) and used as the final formulation in the Phase 3 clinical trials exhibited rapid to very rapid dissolution for BIC, FTC and TAF, and the batches produced by the alternate/additional proposed commercial Drug Product Manufacturer (Gilead/Ireland) exhibited generally very rapid dissolution for all three APIs. Overall, the dissolution profile data provided support the addition of the alternate Drug Product Manufacturing site.

With respect to the BIC drug substance, the proposed commercial manufacturers (Gilead/Canada, and (b) (4)) are the same as used in the manufacture of the Phase 3 clinical batches. Additionally, the proposed commercial FTC and TAF drug substance and intermediate suppliers were either the same as used in the manufacture of the Phase 3 clinical batches or (per the FDA Facility Reviewer) had been previously qualified under cross-referenced NDA 207561 (original) and NDA 021500/Suppl-1.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:
Gerlie Gieser, Ph.D., 9/29/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Elsbeth Chikhale, Ph.D., 10/29/2017

Gerlie Gieser

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Elsbeth Chikhale

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

Final Risk Table for Bictegravir/Emtricitabine/Tenofovir Alafenamide, B/F/TAF (NDA #210251)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**		Acc	
Physical stability (solid state)		**M**	Previous experience with FTC/TAF. Stability results for BIC alone	Acc	
Content uniformity		**M**	Content uniformity release testing per <905>; (b) (4) [redacted] was performed	Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**	Dissolution method had discriminating power and the Applicant has revised acceptance criteria	Acc	
Tablet water content		**L**		Acc	
Drug Product Impurity Control		**M**	Controlled by release and stability specifications; stability results also indicate this risk is mitigated	Acc	

Andrei
Ponta

Digitally signed by Andrei Ponta
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