

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202123Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-123

CompleraTM
(emtricitabine, rilpivirine, and tenofovir disoproxil fumarate) Tablets
200 mg/25 mg/300 mg

Applicant: Gilead Pharmaceuticals, Inc.

Rao V. Kambhampati, Ph.D.

Quality Review #2
For Division of Antiviral Products (DAVP)

Chemistry Review Data Sheet

1. NDA 202-123
2. REVIEW #: 2
3. REVIEW DATE: 8-5-2011
4. REVIEWER: Rao V. Kambhampati
5. PREVIOUS DOCUMENTS:

Previous Documents

NDA 202123 Quality Review

Document Date

7/15/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original 0000

Resubmission 0012

Amendment 0038

Amendment 0040

EDR Date

9/3/2010

2/10/2011

8/3/11

8/4/11

7. NAME & ADDRESS OF APPLICANT:

Name: Gilead Sciences, Inc.

Address: 333 Lakeside Drive, Foster City, CA 94404

Representative: Shalini Gidwani

Telephone: 650-574-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CompleraTM

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): emtricitabine, rilpivirine, and tenofovir disoproxil fumarate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50; 505 (b)(1)

10. PHARMACOL. CATEGORY: Antiviral (anti-HIV 1)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 200 mg/25 mg/300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

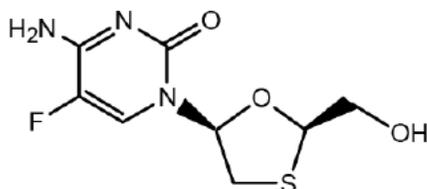
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Emtricitabine:

IUPAC: 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine

CAS: 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)- (1*H*)-pyrimidin-2-one

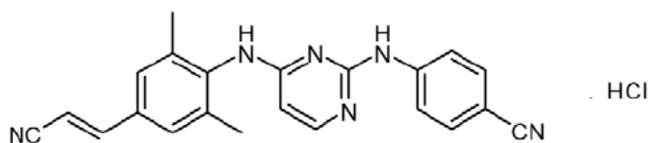


C₈H₁₀FN₃O₃S
247.24

Rilpivirine hydrochloride:

4-[[4-[[4-[(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzotrile monohydrochloride

Chemistry Review Data Sheet



· HCl

C₂₂H₁₈N₆·HCl

402.88 (hydrochloride)

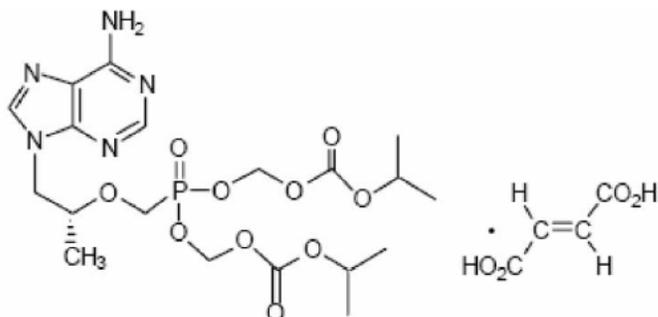
366.42 (free base)

Tenofovir disoproxil fumarate:

IUPAC: 9-[(2-

[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)

CAS: 9-[[2-[(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-2,4,6,8-tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl)ester, 5-oxide, (E)-2-butenedioate (1:1)

C₂₃H₃₄N₅O₁₄P (fumarate)

635.52 (fumarate)

519.44 (free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Rilpivirine hydrochloride	3	Adequate	3/28/11	Reviewed by Maotang Zhou (ONDQA)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

- 6 – DMF not available
- 7 – Other (explain under “Comments”)

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21752	Truvada Tablets
NDA	21356	Viread Tablets
NDA	202022	Edurant Tablets (Tibotec)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	8/5/11	A. Inyard (OC)
ONDQA Biopharm	Acceptable	7/15/11	Elsabeth Chikhale
LNC	Not Applicable	7/15/11	
Methods Validation	Not Applicable	7/15/11	
EA	Acceptable	7/15/11	Rao Kambhampati
Microbiology	Not Applicable	7/15/11	
DMEPA	Acceptable	6/29/11	Irene Chan (DMEPA)

Chemistry Assessment Section

The Chemistry Review #2 for NDA 202-123

The Quality Review #1 was filed in DARRTS on 7/15/11 in order to meet the GRMP dead line. At the time of Review #1 filing, the following compliance issue was pending:

1. The recommendation from the Office of Compliance on the overall acceptability of the manufacturing facilities for this NDA 202-123 was pending.

On 8/2/11, the Office of Compliance (A. Inyard) provided the Overall Recommendation for the facilities of this NDA as "Withhold" (b) (4)

On 8/2/11, a teleconference was held between the FDA and Gilead representatives. In the telecon, Gilead stated that (b) (4) will be removed from the list of facilities that are involved in the manufacturing of emtricitabine drug substance. Also, Gilead stated that an amendment stating this change will be submitted to the NDA.

On 8/3/11, Gilead submitted an amendment #0038 dated 8/3/11 to the NDA and stated the following in the cover letter:

Gilead Sciences, Inc. (Gilead) hereby submits our response to FDA's 02 August 2011 teleconference request. As agreed with FDA, provided in this submission are the revised modules removing reference to the discussed emtricitabine manufacturing facility as it relates to this NDA.

Comments: Gilead clearly did not state which facility they want to remove either in the cover letter or in the revised modules of the amendment dated 8/3/11. However, by reading the modules, it appears that Gilead wants to remove (b) (4) from the list of emtricitabine drug substance manufacturing facilities. A revised Establishment Information-Attachment to Form FDA 356h; revised 2.3.S.2.1 Manufactures (emtricitabine) section; and revised 3.2.S.2.1 Manufacturers (emtricitabine) section were provided in the amendment. A revised emtricitabine drug substance manufacturers list is provided in the Appendix of this review.

The initial NDA submission contained four emtricitabine drug substance manufacturing facilities. (b) (4) the following three facilities are present currently:

(b) (4)

Chemistry Assessment Section

(b) (4)

Upon communication with Gilead through the OND PM, Gilead submitted an amendment dated 8/4/11 in which Gilead stated that they removed the (b) (4) from the revised list.

Then the ONDQA PM requested the EES to remove the (b) (4) facility from the list of facilities for this NDA. The EES removed the (b) (4) facility from the list and issued (A. Inyard, OC) an Overall Recommendation of Acceptable on 8/5/11. A copy of the EER is provided in the Appendix of this review.

Overall Comments: From the Quality (CMC) stand point the NDA 202-123 is recommended for approval.

Primary Reviewer: Rao V. Kambhampati, Ph.D.

Secondary Reviewer: Stephen P. Miller, Ph.D.

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/s/

RAO V KAMBHAMPATI
08/05/2011

STEPHEN P MILLER
08/08/2011

I concur - this NDA is recommended for approval from the CMC perspective

NDA 202-123

CompleraTM
(emtricitabine, rilpivirine, and tenofovir disoproxil fumarate) Tablets
200 mg/25 mg/300 mg

Applicant: Gilead Pharmaceuticals, Inc.

Rao V. Kambhampati, Ph.D.

Quality Review
For Division of Antiviral Products (DAVP)

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Chemistry Review Data Sheet

1. NDA 202-123
2. REVIEW #: 1
3. REVIEW DATE: 7-15-2011
4. REVIEWER: Rao V. Kambhampati
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original 0000	9/3/2010
Amendment 0003	11/9/2010
Amendment 0005	11/30/2010
Amendment 0006	12/3/2010
Amendment 0010	12/23/2010
Amendment 0011	1/27/2011
Resubmission 0012	2/10/2011
Amendment 0013	2/14/2011
Amendment 0023	5/31/2011
Amendment 0025	6/3/2011
Amendment 0027	6/21/2011
Amendment 0029	6/24/2011
Amendment 0030	7/7/2011
Amendment 0032	7/13/2011

7. NAME & ADDRESS OF APPLICANT:

Name:

Gilead Sciences, Inc.

Chemistry Review Data Sheet

Address: 333 Lakeside Drive, Foster City, CA 94404
Representative: Shalini Gidwani
Telephone: 650-574-3000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Complera™
b) Non-Proprietary Name (USAN): emtricitabine, rilpivirine, and tenofovir disoproxil fumarate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

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14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

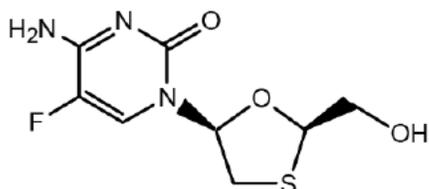
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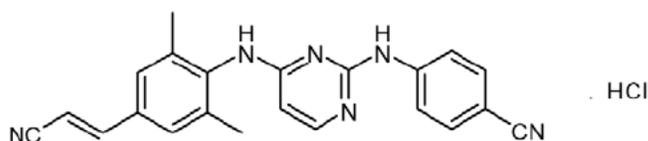
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Chemistry Review Data Sheet

 $C_8H_{10}FN_3O_3S$

247.24

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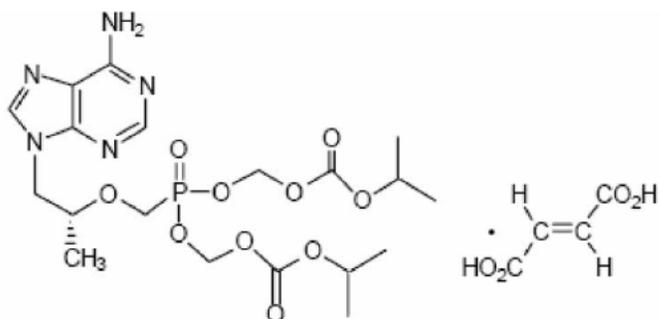
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CAS: (*R*)-5-[[2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]-2,4,6,8,-tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl)ester, 5-oxide, (*E*)-2-butenedioate (1:1) $C_{23}H_{34}N_5O_{14}P$ (fumarate)

635.52 (fumarate)

519.44 (free base)

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Chemistry Review Data Sheet

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NDA	21356	Viread Tablets
NDA	202022	Edurant Tablets (Tibotec)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	7/15/11	DMPQ, OC
ONDQA Biopharm	Acceptable	7/15/11	Elsabeth Chikhale
LNC	Not Applicable	7/15/11	
Methods Validation	Not Applicable	7/15/11	
EA	Acceptable	7/15/11	Rao Kambhampati
Microbiology	Not Applicable	7/15/11	
DMEPA	Acceptable	6/29/11	Irene Chan (DMEPA)

The Chemistry Review for NDA 202-123

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. However, a recommendation from the Office of Compliance on the overall acceptability of the manufacturing facilities has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is recommended for approval pending completion of satisfactory manufacturing inspections.

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

A Post-Marketing Commitment will be established so that the dissolution acceptance criteria will be reevaluated after one year of commercial manufacturing experience.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

Drug Substances: The Complera™ (emtricitabine, rilpivirine, and tenofovir disoproxil fumarate) Tablets, 200 mg/25 mg/300 mg, contain three APIs. All three APIs were previously approved by the FDA for their use in single ingredient drug products (Emtriva Capsules, Emtriva Oral Solution, Edurant Tablets, and Viread Tablets) and fixed dose combination tablets (Truvada Tablets and Atripla Tablets). The CMC information for drug substances was cross-referenced to Gilead's approved NDA #21-752 for emtricitabine drug substance information, (b) (4) DMF (b) (4) for rilpivirine hydrochloride drug substance information, and Gilead's approved NDA #21-356 for tenofovir disoproxil fumarate drug substance information. The DMF (b) (4) was recently reviewed by Maotang Zhou (ONDQA) and it was found to be adequate. In addition, the applicant provided some CMC information directly in the NDA which included nomenclature, structure, general properties, manufacturers, and specification. However, the batch analysis information was not provided in the initial submission (9/3/10). Upon request (6/2/11), COAs were provided for 7 lots of emtricitabine, 5 lots of tenofovir DF, and 6 lots of rilpivirine HCl. (b) (4)

(b) (4) These lots were used for the manufacturing of the stability, clinical, and/or scale-up drug product tablet lots. Upon comment, the emtricitabine drug substance batches that were stored (b) (4) were analyzed for the presence

Executive Summary Section

of (b) (4) impurities and none of the lots contained any detectable level of these impurities. Therefore, the applicant demonstrated that the (b) (4) are not formed in the drug substance at release and during storage. The proposed specifications for all three APIs are same as those approved previously for other NDAs.

Drug Product: The Complera™ (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablet is a fixed-dose combination (FDC) product containing three active pharmaceutical ingredients, emtricitabine (FTC), rilpivirine hydrochloride, and tenofovir disoproxil fumarate (tenofovir DF, TDF). Each tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (RPV, as 27.5 mg of rilpivirine hydrochloride), and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg tenofovir disoproxil (b) (4)). The tablets are capsule shaped, film-coated, purplish-pink, and debossed with “GSP” on one side and plain faced on the other side. The tablets are packaged in 100-mL, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant, and (b) (4) coil. Each bottle is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction sealed, aluminum-faced liner. (b) (4)

(b) (4) Each tablet contains the following inactive ingredients: (b) (4) microcrystalline cellulose, (b) (4) lactose monohydrate, (b) (4) povidone, (b) (4) pregelatinized starch, (b) (4) Polysorbate 20, (b) (4) Croscarmellose Sodium, and (b) (4) magnesium stearate. The tablets are coated with (b) (4) film coat that is made of hypromellose, (b) (4) (FS&C Blue #2) aluminum lake, lactose monohydrate, poly ethyleneglycol, red iron oxide, (b) (4) (FD&C Yellow #6) aluminum lake, titanium dioxide, and triacetin. All the excipients are of compendial grade except the colorant which complies with federal food regulations. The Access Trade Dress (for export) tablets are white, capsule-shaped, film-coated, debossed with “GSP” on both sides and these tablets are coated with (b) (4) that is made of lactose monohydrate, hypromellose, titanium dioxide, and triacetin. (b) (4) (b) (4) the weight of the coated tablet is 1184.5 mg.

The drug product tablets are manufactured by (b) (4). The proposed commercial batch size for manufacture is (b) (4). The manufacturing process includes (b) (4).

(b) (4) In-process testing is applied during the manufacturing process. The critical steps of the process are controlled via equipment operating parameters and testing during the process. The critical process steps and process tests for the identified steps were provided. The robustness of the manufacturing procedure for the clinical bioequivalence and the proposed commercial formulation has been demonstrated by the successful manufacture of representative batches (b) (4). These scale-up experiences led to the final commercial

Executive Summary Section

manufacturing process of the selected formulation. Process validation will be completed (b) (4) and include an expanded sampling plan to demonstrate consistent product quality throughout the unit process steps during the manufacture of each batch. Process validation will be performed prior to commercial distribution of emtricitabine/rilpivirine/tenofovir DF tablets. All excipients used in the manufacture of emtricitabine/rilpivirine/tenofovir DF tablets meet USP/NF and Ph. Eur. standards except for the film-coating material which is tested according to an in-house standard. (b) (4)

(b) (4) None of the excipients are obtained from Human or Animal Origin except lactose monohydrate which is obtained from cow's milk that is fit for human consumption.

The specifications for tablets included appearance, identification by chromatographic retention time, identification by UV spectroscopy, (b) (4) strength, degradation product content, Uniformity of Dosage Units, and dissolution. The initial submission did not contain acceptance criteria for (b) (4) degradants in the shelf-life specification but they were included in the resubmission. On the basis of the batch release, stability data, and statistical analysis of the stability data and comparative stability of the proposed tablets with Truvada and Edurant tablets, the applicant was advised to tighten many of the shelf-life acceptance criteria for the degradation products, and the applicant tightened many of the acceptance criteria and provided adequate justification for the others. See drug product specification section of this review for a detailed discussion on this topic. A description was provided for all the analytical methods and the validation reports were provided for the identity of tablets by UV, identity, strength, and degradation products content of tablets by HPLC, Content Uniformity, and dissolution method. A justification was provided for not including the microbial limits test in the drug product specification on the basis of the microbial test results of the three stability lots at release and at 12 month long-term stability test point. Upon comment, the water activity data and inherent antimicrobial activity information were provided. The batch analysis results were provided for six batches which included pivotal clinical, primary stability, and scale up lots. The results demonstrated that the tablets can be manufactured with consistent quality and purity. The stability data were provided for three registration lots. The data included 12 months long-term (25°C/60%RH and 30°C/75% RH) and 6 months accelerated (40°C/75%RH), comparison of the results with those of Atripla and Truvada tablets, and statistical analysis. On the basis of this information, the applicant suggested an expiration dating period of 24 months when the tablets are stored at 25°C for the US and store below 30°C for alternative trade dress tablets which is acceptable.

B. Description of How the Drug Product is Intended to be Used

Complera™ tablets are indicated for use as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naïve adults. The recommended dose of Complera is one tablet taken once daily with a meal. A bottle of 30 tablets will provide one month supply.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

All three APIs in the Complera™ tablets were previously approved by the FDA for their use in other approved single API containing drug products or fixed dose combination drug products. CMC information for the APIs was cross-referenced to the applicant's previously approved NDAs or contractor's DMF that was found to be adequate by the ONDQA reviewer. The components used in the Complera™ tablets are commonly used in the other approved drug products tablets. (b) (4)

(b) (4) The manufacturing process is robust, (b) (4) and adequate in-process controls are in place. The process has been demonstrated to produce tablets with consistent quality and purity. The drug product's specification is adequate, after revisions submitted in July 7, 2011 amendment. The impurities are controlled at the drug substance stage and the degradants are monitored and controlled in the drug product tablets. The dissolution method is acceptable. However, a Post-Marketing Commitment will be established so that the dissolution acceptance criteria will be reevaluated after one year of commercial manufacturing experience. Adequate stability data were provided to demonstrate the stability of the tablets during the expiration dating period of 24 months, both for the US tablets (purplish-pink film-coat; recommended storage at 25°C) and Access Program version (white film-coat; recommended storage below 30°C). The Tradename, Complera™, is acceptable to the DMEPA. The initially submitted container and carton labels were revised to comply with the current requirements. A total of 15 establishments were provided for this product. All the sites except (b) (4) (b) (4) emtricitabine drug substance manufacturing site were found to be acceptable and an Overall Recommendation for this NDA by the DMPQ (OC) is pending as of 7/15/11. This application does not include any biowaiver.

III. Administrative**A. Primary Reviewer:**

Rao V. Kambhampati, Ph.D.

B. Secondary Reviewer:

Stephen P. Miller, Ph.D.

161 pages has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

RAO V KAMBHAMPATI
07/15/2011

STEPHEN P MILLER
07/15/2011

I concur - this NDA is recommended for approval from the CMC perspective pending completion of satisfactory manufacturing inspections.

Initial Quality Assessment
Branch V
Division of New Drug Quality Assessment II

OND Division: Division of Anti-Viral Products
NDA: 202-123
Applicant: Gilead
Stamp Date: February 10, 2011
Proposed Trademark: Complera™ (*proposed name; currently under review*)
Established Name: Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate fixed-dose combination tablets
Dosage Form: Tablets
Route of Administration: Oral
Strength: 200 mg/25 mg/300 mg
Indication: Treatment of HIV Infection
Reviewer(s): Rao Kambhampati (Chemistry); Elsbeth Chikhale (Biopharmaceutics)
CMC Lead: Dorota Matecka (Acting)

	YES	NO
Acceptable for filing:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Introduction

The proposed fixed dose combination (FDC) tablet of emtricitabine (FTC), rilpivirine (RPV), and tenofovir disoproxil fumarate (TDF) is indicated for the treatment of HIV-1 infection in adults. Each FTC/RPV/TDF FDC tablet contains FTC, RPV, and TDF at the same dosages as recommended for the individual components, i.e., 200 mg of FTC, 25 mg of RPV (as 27.5 mg rilpivirine hydrochloride), and 300 mg of TDF.

This NDA has been submitted in the eCTD format and is available in the EDR. The original submission was a rolling submission with the following CMC relevant amendments:

1. Submission dated September 3, 2010 (Tier 1 -QOS and Module 3; carton and container labels)
2. Submission dated November 9, 2010 (request for proprietary name)
3. Submission dated November 23, 2010 (Tier 3 – Environmental Analysis)
4. Resubmission dated February 10, 2011
5. Submission dated February 14, 2010 (request for proprietary name)

The initial stamp date for this NDA was November 23, 2010; however, the initial action for this NDA was a refuse-to-file (RTF) recommendation (letter dated January 20, 2011) due to the issue of two recently reported degradants of emtricitabine (b) (4). The RTF recommendation for NDA 202-123 was based on the need for (b) (4).

information to establish the safe levels of these degradants and to assure that these impurities are controlled at or below the safe level during storage and use of the drug product. [Further information on this issue is contained in Gilead's December 23, 2010, Request for Comment (NDAs 202-123, 21-752 and 21-937), Gilead's November 11, 2010, background package (e.g., Sequence No. 367 to NDA 21-752) and FDA's meeting minutes for the subsequent December 13, 2010 teleconference with Gilead (documented under NDA 21-752 on December 23, 2010)].

After discussion at a multi-disciplinary meeting on January 7, 2011, it was recognized that comprehensive information on the (b) (4) degradants (planned for submission in late February 2011) was needed to file and review this NDA. Several filing comments were included in the RTF letter. A response to the RTF comments has been submitted in the subsequent NDA 202-123 resubmission (dated February 10, 2011; section 1.11.1. Response to Comment 6 Identified in FDA Refuse to File Letter Dated 20 January 2011 – Reference ID: 2894275).

Per agreements during the February 7, 2011 meeting with the Agency, the applicant retained the original NDA number and was not required to resubmit information previously submitted to this NDA. The adequacy of the overall data submitted previously and in the February 10, 2011 submission will be a review issue; however, based on the overall information provided, this NDA was subsequently considered fileable from the CMC perspective (filing meeting on March 9, 2011).

The new stamp date for this NDA is February 10, 2011. This NDA will be reviewed on a priority (6 month) timeline.

IND Development

The proposed drug product has been developed under IND 106,252.

The discussion and agreements reached during the pre-NDA meeting (June 3, 2010) and CMC-only Type C meeting (June 30, 2010) are available from DARRTS.

Other Applications that are relevant to this review

NDA 202-022 for rilpivirine tablets, 25 mg, currently under review.

NDA 21-752 for Truvada® (tenofovir disoproxil fumarate/emtricitabine) Tablets; 300 mg/200 mg approved August 2, 2004.

NDA 21-356 for Viread® (tenofovir disoproxil fumarate) Tablets, 300 mg, approved on October 26, 2001.

NDA 21-500 for Emtriva® (emtricitabine) Capsules, 200 mg, approved July 3, 2003.

IND 106,252 for tenofovir emtricitabine/rilpivirine/disoproxil fumarate tablets.

IND 67,699 for rilpivirine tablets.

Summary and Critical Issues

Drug Substances

Per agreements at the June 30, 2010 pre-NDA meeting, the applicant cross-referenced other applications for the three drug substances. However, per FDA's request, general information (i.e. section 3.2.S.1) and a specification for each of the drug substances have been provided in the current NDA. In addition, some information was also included in the Pharmaceutical Development (3.2.P.2.1. Components of the Drug Product).

Emtricitabine

Information for emtricitabine drug substance is cross-referenced to NDA 21-752 [Truvada® (emtricitabine/tenofovir disoproxil fumarate) Tablets]. Per agreements during the pre-NDA meeting, a list of emtricitabine drug substance changes submitted to NDA 21-752 since the marketing authorization was granted was submitted in section 1.4.4 of the current NDA.

The manufacturing facilities listed for the emtricitabine drug substance in the current NDA include:

(b) (4)
(b) (4)

NDA 21-572 provides details regarding the chemistry, manufacturing, and controls for emtricitabine drug substance manufactured (b) (4)

(b) (4) described in approved NDA 21-500 for Emtriva (emtricitabine) Capsules.

Rilpivirine Hydrochloride

For information for rilpivirine (TMC 278) drug substance, LoA to DMF Type II (b) (4) and Tibotec's NDA 202-022 have been provided. DMF Type II (b) (4) has been reviewed in support of NDA 202-022 for rilpivirine tablets. This NDA is currently under review in the DAVP. Rilpivirine will be manufactured at (b) (4) (sites submitted in NDA 202-022).

Tenofovir Disoproxil Fumarate

Information for tenofovir drug substance is cross-referenced to NDA 21-752 and NDA 21-356 [Viread® (tenofovir disoproxil fumarate) Tablets]. Per agreements during the pre-NDA meeting, a list of tenofovir disoproxil fumarate drug substance changes submitted to NDA 21-752 since the marketing authorization was granted was submitted in section

1.4.4 of the current NDA. The TDF drug substance will be manufactured at: (b) (4)
(b) (4)
It appears that the first two facilities were approved previously via the original NDA 21-356; (b) (4)

Comment: It would be beneficial to compare the specifications for each drug substance proposed in the current NDA with the respective specifications approved via referenced NDAs (as several manufacturing changes have been made and approved via supplements for both Truvada and Viread products). The manufacturing facilities should also be verified (as described above).

Drug Product

The proposed drug product, FTC/RPV/TDF FDC tablet contains three active pharmaceutical ingredients: 200 mg of emtricitabine, 25 mg rilpivirine (as 27.5 mg of rilpivirine hydrochloride), and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg tenofovir disoproxil (b) (4)). The tablets are capsule shaped, film-coated purplish-pink, and debossed with “GSI” on one side and plain faced on the other side.

FTC/RPV/TDF FDC tablets are (b) (4)
(b) (4) The quantitative composition is presented in Tables 3.2.P.1.2-1 and 3.2.P.1.2-2 (attached below in Appendix I)

All of the excipients within the formulation are compendial, non-novel excipients controlled to the requirements of the current monograph in the USP/NF.

Manufacturing process of FTC/RPV/TDF FDC tablets involves (b) (4)

Executed production records for the manufacturing of emtricitabine/tenofovir disoproxil fumarate powder (b) (4) (Batch Record No. 3800001437), rilpivirine HCl powder (b) (4) (Batch Record No. 3800001439), (b) (4) (Batch Record No. 3800001435), and packaging (Batch Record No. 4800001707) for lot BY1001 of FTC/RPV/TDF have been provided in section 3.2.R.1. Lot BY1001 is a primary stability batch and was manufactured in at (b) (4)

where the emtricitabine/tenofovir disoproxil fumarate powder (b) (4) accounts for (b) (4) and the rilpivirine powder (b) (4) accounts for (b) (4) of the batch.

(b) (4)

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/s/

DOROTA M MATECKA
04/18/2011

STEPHEN P MILLER
04/25/2011

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Checklist

NDA Number: 202-123

Supplement Number and Type:

Established/Proper Name:
*CompleraTM**
(emtricitabine/rilpivirine/tenofovir disoproxil fumarate) fixed-dose combination tablets, 200 mg/25 mg/300 mg

Applicant: Gilead

Letter Date: 10-Feb-2011**

Stamp Date: 10-Feb-2011**

**Proposed trade name (the name request resubmitted via the February 14, 2011 amendment and currently under review).*

***This submission contains responses to the deficiencies outlined in the Refuse-To-File (RTF) letter for this NDA issued on January 20, 2011. Per agreements during the February 7, 2011 meeting with the Agency, the applicant retained the original NDA number and was not required to resubmit information previously submitted to this NDA.*

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		Attachment to FDA Form 356h provided in the February 10, 2011 submission (containing updated contact information).

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.</p>			NA
7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Information for the three drug substances provided in the attachment to FDA Form 356h submitted in the December 3, 2010 amendment (resubmitted in the February 10, 2011 submission).</p>

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Information provided in the attachment to FDA Form 356h submitted in the December 3, 2010 amendment (resubmitted in the February 10, 2011 submission to provide updated contact information).</p>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	✓		<p>Provided in the FDA Form 356h submitted in the December 3, 2010 amendment (reconfirmed in the February 10, 2011 submission).</p>

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		Request for categorical exclusion provided in the submission dated November 23, 2010.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Emtricitabine: cross-reference to NDA 21-752. Tenofovir: cross-reference to NDA 21-356 and NDA 21-752. Rilpivirine drug substance - LoA to DMF Type II (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		Section 3.2.P.3 updated and resubmitted via submission dated February 10, 2011 amendment.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		Section 3.2.P.3 updated and resubmitted via submission dated February 10, 2011 amendment.
21.	Is there a batch production record and a proposed master batch record?	✓		Executed production records for the manufacturing of emtricitabine/tenofovir disoproxil fumarate powder (b) (4) (Batch Record No. 3800001437), rilpivirine HCl powder (b) (4) (Batch Record No. 3800001439), (b) (4) (Batch Record No. 3800001435), and packaging (Batch Record No. 4800001707) for lot BY1001 of FTC/RPV/TDF have been provided in section 3.2.R.1.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?	✓		Section 3.2.P.5 updated and resubmitted via submission dated February 10, 2011 amendment (which includes updated information regarding the (b) (4) impurities).
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		Update (12-month) stability data (including (b) (4) data and statistical analysis data) provided in the February 10, 2011 submission.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			<i>Some description of the formulation and manufacturing process optimization experiments in P.2.</i>

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not obvious.
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		Section 3.2.P.5.3 (resubmitted in the February 10, 2011 amendment).

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		LoA for DMF (b) (4) (rilpivirine HCl) provided in Tier 1 (submission dated September 3, 2010). Information on container/closure system provided in NDA (Tier 1) – no reference to DMF type III noticed.

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		Bottle and carton labels provided in Tier 1 (submission dated September 3, 2011).

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓	<p>The RTF action has been previously recommended for NDA 202-123 based on the lack of information to establish the safe levels of the two recently recognized emtricitabine degradants (b) (4) and to assure that these impurities are controlled at or below the safe level during storage and use of the drug product. Several comments were listed in the RTF letter dated January 20, 2011. These comments were addressed in the current resubmission (dated February 10, 2011). The adequacy of these data will be a review issue; however, based on the new information provided, this NDA can be now considered fileable from the CMC perspective.</p>
35.	<p>If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.</p>	✓	
36.	<p>Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?</p>	✓	

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Dorota Matecka
Acting CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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/s/

DOROTA M MATECKA
03/17/2011

STEPHEN P MILLER
03/17/2011

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Checklist

NDA Number: 202-123 Supplement Number and Type:

Established/Proper Name:
Complera*
(emtricitabine/rilpivirine hydrochloride/tenofovir disoproxil fumarate fixed-dose combination tablets)

200 mg/25 mg/300 mg

Applicant: Gilead Letter Date: 23-Nov-2010 Stamp Date: 23-Nov-2010

**Proposed trade name (under review)*

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		Attachment to FDA Form 356h submitted in the 3-Dec-2010 amendment.

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.</p>			NA
7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Information for the three drug substances provided in the attachment to FDA Form 356h submitted in the 3-Dec-2010 amendment.</p>

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Information provided in the attachment to FDA Form 356h submitted in the 3-Dec-2010 amendment.</p>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	✓		<p>Provided in the FDA Form 356h submitted in the 3-Dec-2010 amendment.</p>

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		Request for categorical exclusion provided in the submission dated 23-Nov-2010.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Emtricitabine: cross-reference to NDA 21-752. Tenofovir: cross-reference to NDA 21-356 and NDA 21-752. Rilpivirine drug substance - LoA to DMF Type II (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		Executed production records for the manufacturing of emtricitabine/tenofovir disoproxil fumarate powder (b) (4) (Batch Record No. 3800001437), rilpivirine HCl powder (b) (4) (Batch Record No. 3800001439), (b) (4) (Batch Record No. 3800001435), and packaging (Batch Record No. 4800001707) for lot BY1001 of FTC/RPV/TDF have been provided in section 3.2.R.1.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?		✓	The Drug Product controls are not complete because the method for controlling two degradants has not been validated, and the qualified (safe) level of those degradants has not been established.
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		Stability update (9-month) provided in the 3-Dec-2010 submission. Another update (12-month data) will be submitted in February 2011 (per pre-NDA agreement with FDA).

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

27.	Does the application contain Quality by Design (QbD) information regarding the DP?			<i>Some description of the formulation and manufacturing process optimization experiments in P.2.</i>
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not obvious.

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		Section 3.2.P.5.3

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		LoA for DMF (b)(4) (rilpivirine HCl) provided in Tier 1 (submission dated 3-Sep-2010). Information on container/closure system provided in NDA (Tier 1) – no reference to DMF type III noted.

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		Bottle and carton labels provided in Tier 1 (submission dated 3-Sep-2010).

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?		✓	See Items 25 and 35.

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	✓	<p>After discussion at a multi-disciplinary meeting on Jan 7, 2011, it was recognized that without the information on the recently-identified (b) (4) (planned for submission in late February 2011), there was not sufficient information to approve this NDA. For this reason, Refuse-To-File is recommended for NDA 202-123 based on the need for information to establish the safe levels of these two recently recognized emtricitabine degradants ((b) (4) and to assure that these impurities are controlled at or below the safe level during storage and use of the drug product. Further information on this issue is contained in Gilead's Dec 23, 2010, Request for Comment (NDAs 202-123, 21-752 and 21-937), Gilead's Nov 11, 2010, background package (e.g., Sequence No. 367 to NDA 21-752) and FDA's meeting minutes for the subsequent Dec 13, 2010, teleconference with Gilead (documented under NDA 21-752 on Dec 23, 2010).</p> <p>Filing comments for the letter have been provided separately to the Project Manager.</p>
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	✓	

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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/s/

STEPHEN P MILLER

01/20/2011

This NDA is not complete for filing

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Checklist

NDA Number: 202-123 Supplement Number and Type:

Established/Proper Name:
*Compera**
**(emtricitabine/rilpivirine
hydrochloride/tenofovir
disoproxil fumarate fixed-dose
combination tablets)**

200 mg/25 mg/300 mg

Applicant: Gilead

Letter Date: 23-Nov-2010

Stamp Date: 23-Nov-2010

**Proposed trade name (under review)*

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		Attachment to FDA Form 356h submitted in the 3-Dec-2010 amendment.

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.</p>			NA
7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Information for the three drug substances provided in the attachment to FDA Form 356h submitted in the 3-Dec-2010 amendment.</p>

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Information provided in the attachment to FDA Form 356h submitted in the 3-Dec-2010 amendment.</p>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	✓		<p>Provided in the FDA Form 356h submitted in the 3-Dec-2010 amendment.</p>

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		Request for categorical exclusion provided in the submission dated 23-Nov-2010.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Emtricitabine: cross-reference to NDA 21-752. Tenofovir: cross-reference to NDA 21-356 and NDA 21-752. Rilpivirine drug substance - LoA to DMF Type II (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		Executed production records for the manufacturing of emtricitabine/tenofovir disoproxil fumarate powder (b) (4) (Batch Record No. 3800001437), rilpivirine HCl powder (b) (4) (Batch Record No. 3800001439), (b) (4) (Batch Record No. 3800001435), and packaging (Batch Record No. 4800001707) for lot BY1001 of FTC/RPV/TDF have been provided in section 3.2.R.1.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		Stability update (9-month) provided in the 3-Dec-2010 submission. Another update (12-month data) will be submitted in February 2011 (per -pre-NDA agreement with FDA).
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			<i>Some description of the formulation and manufacturing process optimization experiments in P.2.</i>

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28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not obvious.
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		Section 3.2.P.5.3

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		LoA for DMF (b) (4) (rilpivirine HCl) provided in Tier 1 (submission dated 3-Sep-2010). Information on container/closure system provided in NDA (Tier 1) – no reference to DMF type III noted.

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		Bottle and carton labels provided in Tier 1 (submission dated 3-Sep-2010).

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	✓		

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36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		✓	<i>Not yet identified (b)(4) issue?)</i>
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{See appended electronic signature page}

Dorota Matecka
Acting CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Stephen Miller, Ph.D.
Acting Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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

/s/

DOROTA M MATECKA
12/21/2010

STEPHEN P MILLER
01/06/2011