

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022577Orig1s000

CHEMISTRY REVIEW(S)

To: NDA 22-577 File
Date: January 17, 2012
From: Rapti D. Madurawe, Ph.D.
Through: Terrance Ocheltree, Ph.D.
Subject: Recommendation of NDA approval with post-marketing commitments

Introduction

The drug product manufacturing process for Viread oral powder consists of. (b) (4)

Dr. Rao's review #1 noted that a small fraction of the granules (b) (4) exhibited super potency. In response to the Agency letter dated Jan-04-2012, Gilead sent additional information on the super potency issue. Dr. Rao's review #2 found the information acceptable and recommended approval of the NDA. This memorandum analyzes the super potency information provided by Gilead and outlines the rationale for recommending approval of the NDA with the addition of two post-marketing commitments (PMC).

Analysis of Gilead's response

(b) (4)

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Rationale for recommendation of NDA approval and PMCs

(b) (4)

The clinical studies that established safety and efficacy were conducted with drug product made by the same process. Viread oral powder is an important drug for treatment of pediatric patients with HIV. From a benefit-risk point of view, the data currently available permits a recommendation of NDA approval. However, as the dosage form is a powder, particle segregation could potentially occur during filling of the powder blend into individual containers, and over the “in-use” period. (b) (4) data from a stratified sampling plan during the powder fill process and from an “in-use” study would provide an added degree of assurance the patient gets the stated strength in a scoop of drug product and strengthen the safety of this NDA. Hence, the Agency has requested Gilead to provide the above data in a post-marketing commitment within 1 year of the NDA action date.

Post Marketing Commitments

The final text may differ slightly from that given below.

PMC-1

During the filling of one commercial full-scale Viread oral powder lot, execute a stratified sampling plan to determine the potency of the powder blend and verify that potency variation does not occur due to segregation. Include individual measurements of strength from at least one single scoop sample per container for containers spanning the full packaging run. Include both individual values and statistical analysis of the data in the study report.

The timetable you submitted on January XX, 2012, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 12/18/2012
Final Report Submission: 01/18/2013

PMC-2

Submit data from a simulated in-use study of strength per scoop where a bottle is exhaustively sampled one scoop at a time. Use a bottle subjected to appropriate simulated shipping conditions so that it is representative of a bottle obtained by a patient. Include data from each scoop sampled and appropriate statistical analysis in the study report.

The timetable you submitted on January XX, 2012, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 12/18/2012
Final Report Submission: 01/18/2013

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

/s/

RAPTI D MADURAWA
01/18/2012

TERRANCE W OCHELTRIE
01/18/2012

NORMAN R SCHMUFF
01/21/2012

NDA 22-577

Viread[®]
(tenofovir disoproxil fumarate)
Oral Powder
40 mg/g of powder

Applicant: Gilead Pharmaceuticals, Inc.

Rao V. Kambhampati, Ph.D.
Branch V/DNDQA II/ONDQA

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

Quality Review #2

1. NDA 22-577
2. REVIEW #: 2
3. REVIEW DATE: 1-17-2012
4. REVIEWER: Rao V. Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedEDR Date

Original 0000

6/16/11

Amendment 0016

12/23/11

Amendment 0017

1/6/12

Amendment 0018

1/11/12

Amendment 0019

1/13/12

Amendment 0020

1/13/12

Amendment 0021

1/16/12

7. NAME & ADDRESS OF APPLICANT:

Name: Gilead Sciences, Inc.

Address: 333 Lakeside Drive, Foster City, CA 94404

Representative: Dara Wambach,
Associate Director, Regulatory Affairs

Telephone: 650-522-5489

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Viread[®] Oral Powder

b) Non-Proprietary Name (USAN): Tenofovir disoproxil fumarate

- c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA 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: Powder

12. STRENGTH/POTENCY: 40 mg/gram of powder

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

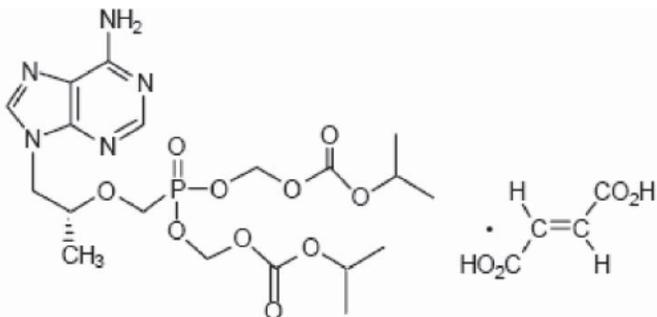
Not a SPOTS product

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

Tenofovir disoproxil fumarate:

IUPAC: 9-[R-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)

CAS: R-5-[[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)



$C_{23}H_{34}N_5O_{14}P$ (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)	(b) (4)	1	Adequate	1/12/12	Reviewed by Rao Kambhampati (ONDQA)
	III			4	Adequate	9/15/2000	Reviewed by Donald Klein (ONDQA)
	III			4	Adequate	5/27/03	Reviewed by Sarah Pope (ONDQA)
	III			4	Adequate		

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

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	21356	Viread Tablets
IND	52849	Tenofovir DF Tablets and Oral Powder

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES for sites inspection recommendation	Acceptable	1/12/12	D. Smith, DGMPA/OMPQ/OC

ONDQA Biopharm for dissolution method	Acceptable	12/12/11	Arzu Selen (ONDQA Biopharm)
LNC (ONDQA)	Acceptable	1/12/12	Richard Lostritto (ONDQA)
Methods Validation	Not Applicable	12/23/11	
EA	Acceptable	11/8/11	Raanan Bloom (OPS)
Product Microbiology	Not Applicable	12/23/11	
DMEPA for Proprietary Name and labels	Acceptable	6/29/11	Irene Chan (DMEPA)
Pharmacology for Safety of Ethylcellulose	Acceptable	12/1/11	Mark Powley, Ph.D. (DAVP)

The Chemistry Review #2 for NDA 22577

The Executive Summary (updated 1/17/12)

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA #22-577 has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The status of DMF (b) (4) referenced for bulk drug product manufacture is adequate. The labels have adequate information as required. The Office of Compliance issued the overall acceptability of the manufacturing facilities as acceptable. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

The applicant committed to the following Post-Marketing Commitments not subjected to the reporting requirements under section 506B:

- 1) During the filling of one commercial full-scale Viread oral powder lot, execute a stratified sampling plan to determine the potency of the powder blend and verify that potency variation does not occur due to segregation. Include individual measurements of strength from at least one single scoop sample per container for containers spanning the full packaging run. Include both individual values and statistical analysis of the data in the study report.

Study/Trial Completion: 12/18/2012

Final Report Submission: 01/18/2013

- 2) Submit data from a simulated in-use study of strength per scoop where a bottle is exhaustively sampled one scoop at a time. Use a bottle subjected to appropriate simulated shipping conditions so that it is representative of a bottle obtained by a patient. Include data from each scoop sampled and appropriate statistical analysis in the study report.

Study/Trial Completion: 12/18/2012

Final Report Submission: 01/18/2013

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

Drug Substance: Viread[®] Oral Powder, 40 mg/gram of powder, contains tenofovir disoproxil fumarate (tenofovir DF) as the active pharmaceutical ingredient (API; drug substance). This API was previously approved by the FDA for its use in single ingredient drug product (Viread[®] Tablets) and in fixed dose combination tablets (Truvada[®] Tablets, Atripla[®] Tablets, and Complera[®] Tablets). The CMC information for the drug substance was cross-referenced to Gilead's approved NDA #21-356 for

Viread adult strength tablets. The proposed specification for the API is same as the one currently approved in NDA 21-356.

Drug Product: Viread® Oral Powder consists of white, taste-masked, microencapsulated granules containing 40 mg of tenofovir DF per gram of powder. Sixty grams of tenofovir DF oral powder is packaged in 250 mL size white HDPE bottles. Each bottle is capped with a white, continuous thread, (b) (4) (b) (4) screw cap with an induction-sealed, aluminum-faced liner. A dosing scoop is packaged with each bottle. Each level dosing scoop delivers approximately one gram of the oral powder (40 mg of tenofovir DF). Each bottle contains 60 g of the oral powder which contains 2.4 g of tenofovir DF, which is equivalent to 1.96 g of tenofovir disoproxil, as active ingredient and the following excipients: (b) (4) g of mannitol (b) (4), (b) (4) g of hydroxypropyl cellulose (b) (4), (b) (4) g of ethylcellulose (b) (4), and (b) (4) g of silicon dioxide (b) (4). The tenofovir DF bulk powder is manufactured by Eurand, Inc. (presently known as Aptalis, Vindalia, OH) and the CMC information was cross-referenced to Eurand's DMF # (b) (4). Some CMC information was also directly provided in the NDA and hence discussed in this NDA review. Batch formula was provided for a (b) (4) batch, which is also the intended commercial size. Tenofovir DF oral powder is manufactured by (b) (4)

(b) (4)
Gilead referenced to (b) (4) DMF (b) (4) for details of the controls of critical steps and intermediates used in the manufacture of bulk tenofovir DF oral powder. The critical steps of the process are controlled via equipment operating parameters and testing during the process. Appropriate control of the process is confirmed by (b) (4)

(b) (4) For the NDA batches, the packaging of bulk powder in bottles was performed by Eurand or (b) (4) and for the validation batch and for the commercial batches, the bulk oral powder is (b) (4) packaged by Gilead Sciences Limited (Carrigtohill, County Cork, Ireland). The specification for the oral powder included Appearance (white to off-white powder), identification (HPLC and UV), strength (HPLC), degradation product content (HPLC), content uniformity, uniformity of mass of delivered doses from multi-dose containers, minimum fill, and dissolution. Upon comment, in the amendment dated 11/23/11, the applicant revised the acceptance criterion in the dissolution method to $Q = (b) (4)$ dissolved at 60 min, which is acceptable to this reviewer and ONDQA Biopharm reviewer (Arzu Selen, Ph.D.). Upon comment, in the amendment dated 12/8/11, the applicant submitted the revised specification with tightened acceptance criteria for total degradation products content, major degradation product content, and some other individual (specified) degradation products contents and the revised specification is acceptable. Analytical procedures and method validation reports were provided for all non-compendial methods. Batch analysis results were provided for 7 batches. The bulk powder was manufactured by Eurand. Five batches were manufactured by Eurand and the remaining two batches were packaged by (b) (4). The drug substance used for these drug product batches was manufactured by either (b) (4) or (b) (4). It was demonstrated that the drug product can be manufactured with consistent quality

and purity. Stability studies were performed on three registration batches under long-term (25°C/60%RH, 36 months), intermediate (30°C/65%RH; 24 months), and accelerated conditions (40°C/75%RH). Also, photostability study (per ICH) and storage in open container (6 weeks) study were performed on one batch. On the basis of the 36-months long-term data, the applicant requested for an expiration dating period of 36 months with a recommended storage condition of “store at 25 °C (77°F) with excursions permitted to 15-30°C (59-86°F)”, which is acceptable. This application does not include any biowaiver.

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

For the treatment of HIV-1 in pediatric patients 2 years of age and older, the recommended oral dose of VIREAD oral powder is 8 mg of tenofovir disoproxil fumarate per kilogram of body weight (up to a maximum of 300 mg) once daily administered as oral powder. VIREAD oral powder should be measured with the supplied dosing scoop. One level dosing scoop delivers approximately 1 g of powder which contains 40 mg of tenofovir disoproxil fumarate, which is equivalent to 33 mg of tenofovir disoproxil. VIREAD oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g., applesauce, baby food, or yogurt). The entire mixture should be ingested immediately. VIREAD oral powder should not be administered in a liquid (e.g., juice) since the powder floats on the liquid and the mixture may produce a bitter taste.

Each bottle contains 60 g of the powder containing a total of 2.40 g of tenofovir disoproxil fumarate, which is equivalent to 1.96 g of tenofovir disoproxil.

C. Basis for Approvability or Not-Approval Recommendation

The API in Viread Oral Powder was previously approved by the FDA for its use in other approved single API containing drug products or fixed dose combination drug products. CMC information for the API was cross-referenced to the applicant’s previously approved NDA #21-356. The tenofovir DF bulk oral powder manufacturing was cross-referenced to the DMF (b)(4) and the DMF was reviewed and found to be adequate. The components used in the drug product are commonly used in the other approved drug products. However, the amount of ethylcellulose consumed by the patient at the highest drug dose (7.5 scoops) would be approximately (b)(4) per day and the safety of the ethylcellulose dose in pediatric patients was assessed by Mark Powley, Ph.D. (Pharmacology/Toxicology Reviewer, DAVP) and Dr. Powley determined that the dose is reasonably safe. The manufacturing process is robust, scaled up to the full production size, and adequate in-process controls are in place. The drug product’s revised specification is adequate. The impurities are controlled at the drug substance stage and the degradants are monitored and controlled in the drug product. The dissolution method and revised acceptance criterion are acceptable. Adequate stability data were provided to demonstrate the stability of the powder during the expiration dating period of 36 months when stored at 25°C. The Tradename, Viread®, is same as the one approved for adult 300 mg strength tablets. The initially submitted container and carton labels were revised to comply with the current requirements. The strength of the drug product on the final revised container and carton labels was

changed from (b) (4) to “40 mg/scoop” upon recommendation by the DMEPA. A total of 7 establishments were provided for this product. The status of all the manufacturing, packaging and testing sites is acceptable and an Overall Recommendation of Acceptable was issued for this NDA by the Office of Compliance.

III. Administrative

A. Primary Reviewer:

Rao V. Kambhampati, Ph.D.

B. Secondary Reviewer:

Rapti Madurawe, Ph.D.

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/s/

RAO V KAMBHAMPATI
01/17/2012

RAPTI D MADURawe
01/18/2012

CHEMIST REVIEW #2
OF Efficacy Supplement
Priority Review – 6-month

1. **ORGANIZATION:** ONDQA-Division II
2. **NDA/SUPP NUMBER:** 21-356 S-038
3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 16-Jun-2011
UN status
Original PDUFA Date: 16-Dec-2011
Revised PDUFA Date: 18-Jan-2011
4. **AMENDMENTS:** 7-Jul-2011; 22-Dec-2011
22-Dec-2012
5. **RECEIVED BY CHEMIST:** June 2011

6. **NDA HOLDER/ ADDRESS**

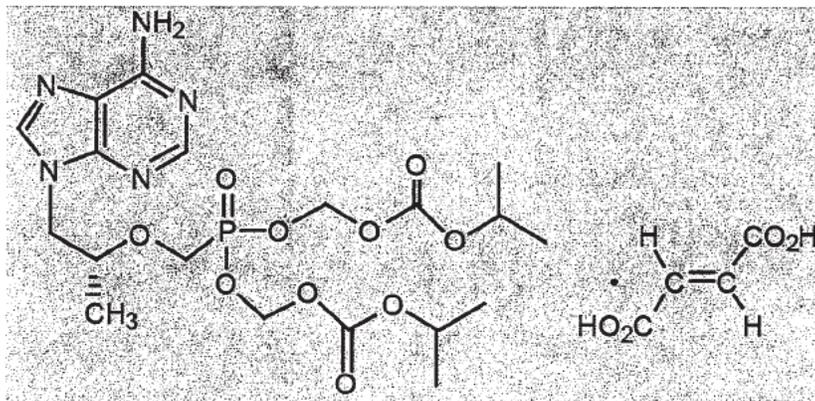
Gilead Sciences
Foster City, CA

7. **SUPPLEMENT PROVIDES FOR:** the addition of three Viread (tenofovir disoproxil fumarate) lower strength tablets, 150 mg, 200 mg, and 250 mg, and the addition of (b) (4) as a drug product stability testing site.

8. **DRUG PRODUCT:** Viread

9. **NONPROPRIETARY NAME:** Tenofovir disoproxil fumarate Tablets

10. **DRUG SUBSTANCE:** Tenofovir disoproxil fumarate



11. **DOSAGE FORM/STRENGTH:** Tablet
12. **ROUTE OF ADMINISTRATION:** Oral
13. **INDICATION:** Treatment of HIV Infection
14. **HOW DISPENSED:** Rx

15. **RELATED IND/NDA/DMF:** 22-577 Viread Oral Powder

16. **COMMENTS:**

This efficacy supplement provides for the addition of three Viread (tenofovir disoproxil fumarate) lower strength tablets, 150 mg, 200 mg, and 250 mg, and the addition of (b) (4) as a drug product stability testing site. The lower strength tablets will be manufactured with the chemistry, manufacturing and controls approved for the 300-mg tablet, with the following exception, that the dissolution test acceptance criterion is $Q = (b) (4)$ in 20 minutes.

Chemistry review #2 evaluates the carton/container label, and revised labeling, received 22-Dec-2011.

17. **CONCLUSIONS AND RECOMMENDATIONS**

The information/data provided support the proposed addition of three lower strength Viread tablets. Additionally, the proposed testing site, (b) (4) was found to be acceptable by the Office of Compliance. This supplement, therefore, is recommended for approval.

18. **REVIEWER NAME**

J. Salemme, Ph.D., chemistry reviewer

DATE COMPLETED

2-Jan-2012

PM: J. David, ONDQA

Branch Chief: Dr. T. Oliver, ONDQA, Division II

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/s/

JEAN SALEMME
01/11/2012

THOMAS F OLIVER
01/12/2012

NDA 22-577

Viread[®]
(tenofovir disoproxil fumarate)
Oral Powder
40 mg/g of powder

Applicant: Gilead Pharmaceuticals, Inc.

Rao V. Kambhampati, Ph.D.
Branch V/DNDQA II/ONDQA

Quality Review
For Division of Antiviral Products (DAVP)

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Chemistry Review Data Sheet

1. NDA 22-577
2. REVIEW #: 1
3. REVIEW DATE: 12-23-2011
4. REVIEWER: Rao V. Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>EDR Date</u>
Original 0000	6/16/11
Amendment 0002	7/18/11
Amendment 0005	9/13/11
Amendment 0006	9/27/11
Amendment 0009	10/10/11
Amendment 0010	10/12/11
Amendment 0011	10/11/11
Amendment 0012	11/3/11
Amendment 0013	11/23/11
Amendment 0014	12/8/11

7. NAME & ADDRESS OF APPLICANT:

Name: Gilead Sciences, Inc.
Address: 333 Lakeside Drive, Foster City, CA 94404
Representative: Dara Wambach,
Associate Director, Regulatory Affairs

Chemistry Review Data Sheet

Telephone:

650-522-5489

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Viread[®] Oral Powder
- b) Non-Proprietary Name (USAN): Tenofovir disoproxil fumarate
- c) Code Name/# (ONDQA 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: Powder

12. STRENGTH/POTENCY: 40 mg/gram of powder

13. ROUTE OF ADMINISTRATION: Oral

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

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

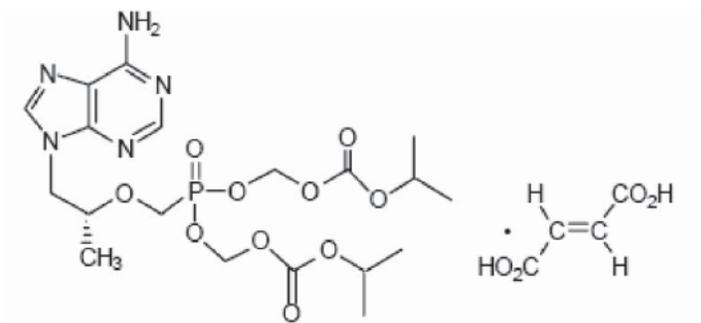
Tenofovir disoproxil fumarate:

IUPAC: 9-[R-2-

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

CAS: R-5-[[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)

Chemistry Review Data Sheet



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)	(b) (4)	1	Pending	12/22/11	Rao Kambhampati (ONDQA)
	III			4	Adequate	9/15/2000	Reviewed by Donald Klein (ONDQA)
	III			4	Adequate	5/27/03	Reviewed by Sarah Pope (ONDQA)
	III			4	Adequate		

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

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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21356	Viread Tablets
IND	52849	Tenofovir DF Tablets and Oral Powder

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES for sites inspection recommendation	Pending	12/23/11	OMPQ, OC
ONDQA Biopharm for dissolution method	Acceptable	12/12/11	Arzu Selen (ONDQA Biopharm)
LNC	Not Applicable	12/23/11	
Methods Validation	Not Applicable	12/23/11	
EA	Acceptable	11/8/11	Raanan Bloom (OPS)
Product Microbiology	Not Applicable	12/23/11	
DMEPA for Proprietary Name and labels	Acceptable	6/29/11	Irene Chan (DMEPA)
Pharmacology for Safety of Ethylcellulose	Acceptable	12/1/11	Mark Powley, Ph.D. (DAVP)

The Chemistry Review for NDA 22577

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 status of DMF (b) (4) referenced for bulk drug product manufacture is pending because Holder's response to an Agency Information Request (IR)/deficiency letter is pending. 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 and adequate status of DMF (b) (4).

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

Drug Substance: Viread[®] Oral Powder, 40 mg/gram of powder, contains tenofovir disoproxil fumarate (tenofovir DF) as the active pharmaceutical ingredient (API; drug substance). This API was previously approved by the FDA for its use in single ingredient drug product (Viread[®] Tablets) and in fixed dose combination tablets (Truvada[®] Tablets, Atripla[®] Tablets, and Complera[®] Tablets). The CMC information for the drug substance was cross-referenced to Gilead's approved NDA #21-356 for Viread adult strength tablets. The proposed specification for the API is same as the one currently approved in NDA 21-356.

Drug Product: Viread[®] Oral Powder consists of white, taste-masked, microencapsulated granules containing 40 mg of tenofovir DF per gram of powder. Sixty grams of tenofovir DF oral powder is packaged in 250 mL size white HDPE bottles. Each bottle is capped with a white, continuous thread, (b) (4) (b) (4) screw cap with an induction-sealed, aluminum-faced liner. A dosing scoop is packaged with each bottle. Each level dosing scoop delivers approximately one gram of the oral powder (40 mg of tenofovir DF). Each bottle contains 60 g of the oral powder which contains 2.4 g of tenofovir DF, which is equivalent to 1.96 g of tenofovir disoproxil, as active ingredient and the following excipients: (b) (4) g of mannitol (b) (4), (b) (4) g of hydroxypropyl cellulose (b) (4), (b) (4) g of ethylcellulose (b) (4), and (b) (4) g of silicon dioxide (b) (4). The tenofovir DF bulk powder is

Executive Summary Section

manufactured by Eurand, Inc. (presently known as Aptalis, Vindalia, OH) and the CMC information was cross-referenced to Eurand's DMF # (b) (4). Some CMC information was also directly provided in the NDA and hence discussed in this NDA review. Batch formula was provided for a (b) (4) batch, which is also the intended commercial size. Tenofovir DF oral powder is manufactured by (b) (4)

Gilead referenced to (b) (4) DMF (b) (4) for details of the controls of critical steps and intermediates used in the manufacture of bulk tenofovir DF oral powder. The critical steps of the process are controlled via equipment operating parameters and testing during the process. Appropriate control of the process is confirmed by (b) (4)

For the NDA batches, the packaging of bulk powder in bottles was performed by Eurand or (b) (4) and for the validation batch and for the commercial batches, the bulk oral powder is (b) (4) packaged by Gilead Sciences Limited (Carrigtohill, County Cork, Ireland). The specification for the oral powder included Appearance (white to off-white powder), identification (HPLC and UV), strength (HPLC), degradation product content (HPLC), content uniformity, uniformity of mass of delivered doses from multi-dose containers, minimum fill, and dissolution. Upon comment, in the amendment dated 11/23/11, the applicant revised the acceptance criterion in the dissolution method to $Q = (b) (4)$ dissolved at 60 min, which is acceptable to this reviewer and ONDQA Biopharm reviewer (Arzu Selen, Ph.D.). Upon comment, in the amendment dated 12/8/11, the applicant submitted the revised specification with (b) (4) acceptance criteria for total degradation products content, major degradation product content, and some other individual (specified) degradation products contents and the revised specification is acceptable. Analytical procedures and method validation reports were provided for all non-compendial methods. Batch analysis results were provided for 7 batches. The bulk powder was manufactured by Eurand. Five batches were manufactured by Eurand and the remaining two batches were packaged by (b) (4). The drug substance used for these drug product batches was manufactured by either (b) (4) or (b) (4). It was demonstrated that the drug product can be manufactured with consistent quality and purity. Stability studies were performed on three registration batches under long-term (25°C/60%RH, 36 months), intermediate (30°C/65%RH; 24 months), and accelerated conditions (40°C/75%RH). Also, photostability study (per ICH) and storage in open container (6 weeks) study were performed on one batch. On the basis of the 36-months long-term data, the applicant requested for an expiration dating period of 36 months with a recommended storage condition of "store at 25 °C (77°F) with excursions permitted to 15-30°C (59-86°F)", which is acceptable. This application does not include any biowaiver.

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

For the treatment of HIV-1 in pediatric patients 2 years of age and older, the recommended oral dose of VIREAD oral powder is 8 mg of tenofovir disoproxil fumarate per kilogram of body weight (up to a maximum of 300 mg) once daily

Executive Summary Section

administered as oral powder. VIREAD oral powder should be measured with the supplied dosing scoop. One level dosing scoop delivers approximately 1 g of powder which contains 40 mg of tenofovir disoproxil fumarate. VIREAD oral powder should be mixed in a container with 2 to 4 ounces of soft food not requiring chewing (e.g., applesauce, baby food, and yogurt). The entire mixture should be ingested immediately. VIREAD oral powder should not be administered in a liquid (e.g., juice) since the powder floats on the liquid and the mixture may produce a bitter taste.

Each bottle contains 60 g of the powder containing a total of 2.40 g of tenofovir disoproxil fumarate, which is equivalent to 1.96 g of tenofovir disoproxil.

C. Basis for Approvability or Not-Approval Recommendation

The API in Viread Oral Powder was previously approved by the FDA for its use in other approved single API containing drug products or fixed dose combination drug products. CMC information for the API was cross-referenced to the applicant's previously approved NDA #21-356. The tenofovir DF bulk oral powder was cross-referenced to the DMF (b) (4). Some comments were conveyed to the Holder and the response from Holder is pending. However, at this point the current data demonstrates that the powder can be manufactured with reasonably consistent quality and purity. The components used in the drug product are commonly used in the other approved drug products. However, the amount of ethylcellulose consumed by the patient at the highest drug dose (7.5 scoops) would be approximately (b) (4) per day and the safety of the ethylcellulose dose in pediatric patients was assessed by Mark Powley, Ph.D. (Pharmacology/Toxicology Reviewer, DAVP) and Dr. Powley determined that the dose is reasonably safe. The manufacturing process is robust, scaled up to the full production size, and adequate in-process controls are in place. The drug product's revised specification is adequate. The impurities are controlled at the drug substance stage and the degradants are monitored and controlled in the drug product. The dissolution method and revised acceptance criterion are acceptable. Adequate stability data were provided to demonstrate the stability of the powder during the expiration dating period of 36 months when stored at 25°C. The Tradename, Viread[®], is same as the one approved for adult 300 mg strength tablets. The initially submitted container and carton labels were revised to comply with the current requirements. A total of 7 establishments were provided for this product. The status of bulk powder manufacturing site, Aptalis (formerly known as Eurand), and drug product packaging site (Gilead, Ireland) is pending as of this review date. The Overall Recommendation for this NDA by the OMPQ (OC) is pending as of this review date.

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

Rao V. Kambhampati, Ph.D.

B. Secondary Reviewer:

Rapti Madurawe, Ph.D.

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/s/

RAO V KAMBHAMPATI
12/23/2011

RAPTI D MADURawe
12/23/2011

CHEMIST REVIEW
OF Efficacy Supplement
Priority Review – 6-month

1. **ORGANIZATION:** ONDQA-Division II
2. **NDA/SUPP NUMBER:** 21-356 S-038
3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 16-Jun-2011
UN status
Original PDUFA Date: 16-Dec-2011
Revised PDUFA Date: 18-Jan-2011
4. **AMENDMENTS:** 7-Jul-2011; 22-Dec-2011
5. **RECEIVED BY CHEMIST:** June 2011

6. **NDA HOLDER/ ADDRESS**

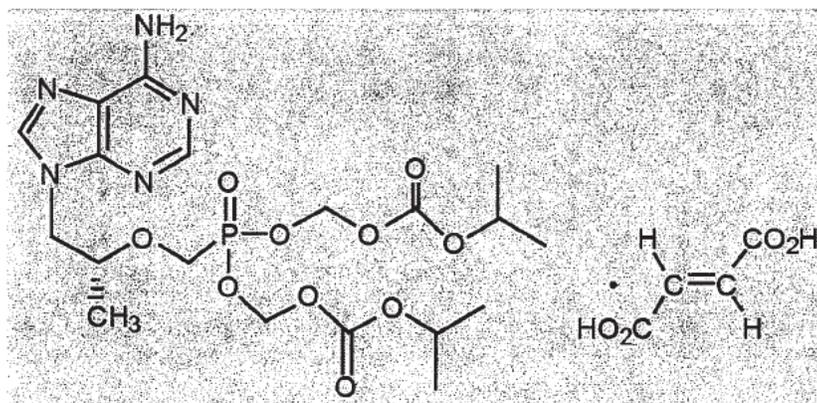
Gilead Sciences
Foster City, CA

7. **SUPPLEMENT PROVIDES FOR:** the addition of three Viread (tenofovir disoproxil fumarate) lower strength tablets, 150 mg, 200 mg, and 250 mg, and the addition of (b) (4) as a drug product stability testing site.

8. **DRUG PRODUCT:** Viread

9. **NONPROPRIETARY NAME:** Tenofovir disoproxil fumarate Tablets

10. **DRUG SUBSTANCE:** Tenofovir disoproxil fumarate



11. **DOSAGE FORM/STRENGTH:** Tablet
12. **ROUTE OF ADMINISTRATION:** Oral
13. **INDICATION:** Treatment of HIV Infection
14. **HOW DISPENSED:** Rx
15. **RELATED IND/NDA/DMF:** 22-577 Viread Oral Powder

16. COMMENTS:

This efficacy supplement provides for the addition of three Viread (tenofovir disoproxil fumarate) lower strength tablets, 150 mg, 200 mg, and 250 mg, and the addition of (b) (4) (b) (4) as a drug product stability testing site. The lower strength tablets will be manufactured with the chemistry, manufacturing and controls approved for the 300-mg tablet, with the following exception, that the dissolution test acceptance criterion is Q= (b) (4) in 20 minutes.

The final carton/container label has not been received. Chemistry review #2 will evaluate the carton/container label.

17. CONCLUSIONS AND RECOMMENDATIONS

The information/data provided support the proposed addition of three lower strength Viread tablets. Additionally, the proposed testing site, (b) (4) was found to be acceptable by the Office of Compliance. This supplement, therefore, is recommended for approval.

Action: Issue an Approval Letter.

18. REVIEWER NAME

J. Salemme, Ph.D., chemistry reviewer

DATE COMPLETED

22-Dec-2011

PM: J. David, ONDQA

Branch Chief: Dr. T. Oliver, ONDQA, Division II

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/s/

JEAN SALEMME
12/22/2011

THOMAS F OLIVER
12/22/2011

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)

FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number:	NDA Type:	Established/Proper Name:
22-577	Original NDA, 505(b)(1)	Viread (Tenofovir Disoproxyl Fumarate) Oral Powder, 40mg/g
Applicant:	Letter Date: June 29, 2011	GRMP Goal: approx Dec 6, 2011
Gilead	Stamp Date: June 30, 2011	PDUFA Goal: Dec 30, 2011

CMC Reviewer: Rao Kambhampati Ph.D.

Biopharmaceutics Reviewer: Arzu Selen, Ph.D.

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?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		All relevant manufacturing sites are described in Section 1.1.2
6.	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.			NA

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

7.	<p>Are drug substance 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) 	X		All relevant manufacturing sites are described in Section 1.1.2
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) 	X		All relevant manufacturing sites are described in Module 3 Section P3 and in Section 1.1.2

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

9.	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: <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) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		On June 16, 2011 Form 356h

* 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.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Fate and Effect data have been consulted to R. Bloom (OPS) for review.

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		X	Refers to NDA 21-356 for this information
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to NDA 21-356 for this information
14.	Does the section contain information regarding the characterization of the DS?	X		Some information in 3.2.P.2.1
15.	Does the section contain controls for the DS?	X		The DS specification is provided via a hyperlink in 3.2.R.2 "incorporated by cross-reference to NDA 21-356" A summary of all DS-related supplements since the approval of the original NDA is in Section 1.4.4
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to NDA 21-356 for this information
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)

FILING REVIEW FOR NDA or Supplement (ONDQA)

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?		X	Refers to DMF (b) (4) for manufacturing processes steps up to the bulk powder blend. A short description of final packaging is given in 3.2.P.3.32 along with a flow chart summarizing the full process.
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?	X		Refers to DMF (b) (4) for details of the manufacturing processes steps up to the bulk powder blend. A short summary of critical controls is included in 3.2.P.3.4, and a short summary of the approach to process validation is in 3.2.P.3.3 Full descriptions of the analytical methods for the DP and validation reports are included in the NDA.
21.	Is there a batch production record and a proposed master batch record?		X	Refers to DMF (b) (4) for master batch records. One packaging record is provided.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Formulation Development is included in Module 3 Section P2
23.	Have any Comparability Protocols been requested?		X	None in 3.2 R. (Regional Information)
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		Bottle (250-mL HDPE) of 60 g of powder Clear (b) (4) scoop to contain 2.1 mL (1 gram) of powder, equivalent to 40 mg of tenofovir DF.
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		36-month data at 25°C/60% RH and 24-mo data at 30°C/65%RH, plus accelerated, open-dish, and photostability studies to support a proposed 36 mo expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		A design space for the DP manufacturing process is included in 3.2.P.2.3

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small
Molecule)**
FILING REVIEW FOR NDA or Supplement (ONDQA)

28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not in the NDA
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PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

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?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2		(b) (4)	6/1/2011	DP manufacturing process
	3			6/1/2011	
2 other Type 3 DMFs are listed in section 1.4.1 for packaging components					

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		Section 1.14; includes dosing table for lower strength tablets (NDA 21-356 / S-038), as well
33.	Have the immediate container and carton labels been provided?	X		Bottle Label and Carton Label for 60 g bottles

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		Dissolution method and data in NDA 22-577 for Viread oral powder and in NDA 21-356 (S038) for Viread (tenofovir disoproxoyl fumarate, TDF) tablets (150, 200 and 250-mg strengths). Since Viread reduced strength tablet is submitted for pediatric indication, both powder and tablet information is mentioned briefly in this section.
35.	Is the dissolution test part of the DP specifications?	X		The proposed dissolution specification for TDF from the Viread oral powder is $Q = (b)(4)$ at 45 minutes. <i>For review, it is stated that "The dissolution profiles clearly show that the rate of dissolution is directly related to the microencapsulation level of the granules."</i> The proposed dissolution specification for TDF from the Viread tablets is $Q = (b)(4)$ at 30 minutes.
36.	Does the application contain the dissolution method development report?	X		Method for Viread powder: USP 2, 100 rpm. Medium: 900 mL of 0.2% polysorbate 80 in 0.01 N HCl at 37 °C. Method for Viread tablet: USP 2, 50 rpm Medium: 900 mL 0.02 N HCl, no surfactant, at 37 °C
37.	Is there a validation package for the analytical method and dissolution methodology?	X		For the Viread powder (NDA 022-577) : The validation of analytical procedures is in 3.2.P.5.3 of the NDA. Method TM-112.01 is provided for the analytical method and method TM-115.02 is provided for dissolution testing of tenofovir DF oral powder. The analytical method report (TM-112.01) includes characterization of system suitability (repeatability, theoretical plates, Tailing Factor and resolution), identity, strength and degradation product content determination. Additional analytical method validation reports on Strength and Content Uniformity of Tenofovir DF Oral Powder and In-Process Samples, and Identity of Tenofovir DF Oral Powder by UV Spectrophotometry are also provided.

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

38.	Does the application include a biowaiver request?	X		Available information for biowaiver assessment for the tablets: 1) Composition proportionality of the 150-, 200- and 250-mg tablets to the approved 300-mg tablet 2) Comparative dissolution data
39.	Does the application include a IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?			Not for filing consideration: The Sponsor states that TDF is highly soluble but poorly permeable: BCS 3
41.	Is information on mixing Viread powder n soft foods and/or drinks provided?	X		For review: “TDF does not mix well with liquids, but floats on top of liquids even after stirring.” Information on mixing Viread powder with soft foods such as applesauce, yogurt, a smoothie, baby food, and pudding is provided.
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		This part of the submission will be reviewed by the Office of Clinical Pharmacology.

PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

K. FILING CONCLUSION				
	Parameter	Yes	No	Comment
43.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
44.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Fileable
45.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Fileable
46.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	No comments from the biopharmaceutics or CMC perspectives for the 74-day letter.

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small
Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

{See appended electronic signature page}

Stephen Miller, Ph.D.
CMC-Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Arzu Selen, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Lead
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

Date

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/s/

STEPHEN P MILLER
08/12/2011

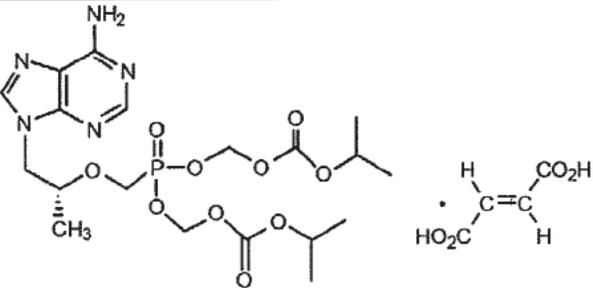
ARZU SELEN
08/15/2011

ANGELICA DORANTES
08/15/2011

RAPTI D MADURawe
08/16/2011

ONDQA Pre-Marketing Assessment Division II
Branch V
Supplement IQA

NDA 21-356 / S-038 (EDR Doc 640) **Efficacy Supplement**
Viread (Tenofovir Disoproxyl Fumarate) Tablets,
150 mg, 200 mg, and 250 mg
Submission Date: June 16, 2011
Date of IQA: July 12, 2011
Review Timeline: 6-Months

	<p>Nucleotide / Nucleoside Prodrug Inhibits HIV Reverse Transcriptase (after conversion to the triphosphate analog)</p>
Tenofovir Disoproxyl Fumarate	New Reduced-Strength Tablets

Summary:

- Adult-strength 300 mg tablet approved in 2001 for treatment of HIV infection
- Many combination products contain this active plus other HIV meds
- These 3 lower-strength tablets plus a new NDA for Viread Oral Powder (22-577) are in response to FDA's pediatric written request
- Reclassified from CMC supplement to Efficacy supplement on July 8, so that a clinical use can be approved in labeling with same time-line as Oral Powder NDA.
- Formulation is same as approved 300 mg strength, (b) (4)
- I did not find any emphasis on QbD, and given the similarity to the approved 300 mg tablet the process development section and the descriptions of the manufacturing process are streamlined.
- Three registration batches at (b) (4)
- Stability data includes the 30degC/75%RH long-term condition that is recommended by FDA and WHO for products that may be used in climatic zones III (hot/dry), Via (hot/humid) and IVb (hot / very humid). Long-term condition of 25degC/60%RH is a backup that is only tested if an OOS result is likely at the more stressful 30/75%RH condition. Accelerated is the normal 40degC/75%RH

for 6 months. This is the usual pattern for PEPFAR NDAs and Gilead “Access Program” products.

- A stability update with 6 months of data was submitted on July 7 (EDR #642) as agreed to during Pre-supplement meeting; a 24-month expiration dating period is proposed, based on what Gilead believes is equivalent stability to the 300 mg tablet.
- Matrixing across the 3 strengths is done at the 9, 12 and 18 mo time points
- I did not find anything to suggest that a separate version of the tablets for use outside the US (“Gilead Access Program”) is included in this supplement.
- The tablets are not scored (dose is 1 tablet/day); 150 mg is triangular-shaped!
- Single packaging configuration: bottles of 30 with desiccant
- No sign of any Comparability Protocols in Module 3 – Regional Info
- Draft bottle labels are provided; the strength is expressed as the salt (older approach) which is consistent with the labeling of other tenofovir disoproxil fumarate products. Recent Clinical discussion for NDA 202-123 favored keeping the strength expression consistent with older products. An equivalency statement is included on the bottle labels.
- The Prescribing Info is at present cross-referring to the Oral Powder NDA (22-577). Gilead has already been asked to submit a copy of the PI to this supplement, and it was submitted on July 11. The reduced-strength tablets are described in that PI, and a dosing table shows the recommended number of tablets that children in different weight ranges should take.
- Recent reviewers of this NDA:
 - Hamid Shafiei (several suppls)
 - Jean Salemme
 - Sharon Kelly
 - Rao Kambhampati (Oral Powder and orig NDA)
- Contains Biowaiver - Arzu Selen is the reviewer for this supplement and for the Oral Powder NDA

Conclusion: This supplement is complete for filing from the CMC perspective.

Stephen P. Miller, Ph.D.
CMC-Lead

See DARRTS
Date

Thomas F. Oliver, Ph.D.
Branch Chief

See DARRTS
Date

DARRTS cc: OND Project Manager
 OND Medical Officer
 ONDQA Project Manager

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/s/

STEPHEN P MILLER
07/14/2011

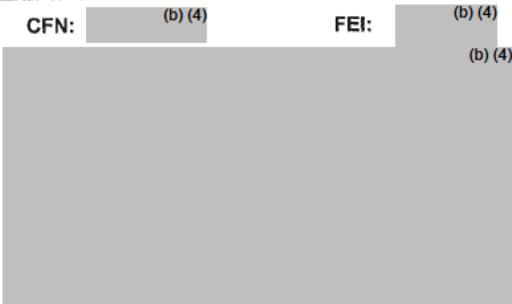
THOMAS F OLIVER
07/14/2011

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22577/000	Sponsor:	GILEAD
Code:	530		333 LAKESIDE DR
Priority:	3Y		FOSTER CITY, CA 94404
Stamp Date:	16-JUN-2011	Brand Name:	TENOFOVIR DISOPROXIL FUMARATE 40 MG
PDUFA Date:	18-JAN-2012	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:		Product Number; Dosage Form; Ingredient; Strengths	001; POWDER; TENOFOVIR DISOPROXIL FUMARATE; 40MG

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	R. KAMBHAMPATI	Review Chemist	301-796-1382
	S. MILLER	Team Leader	301-796-1418

Overall Recommendation:	ACCEPTABLE	on 12-JAN-2012	by D. SMITH	()
	PENDING	on 28-JUN-2011	by EES_PROD	
	PENDING	on 28-JUN-2011	by EES_PROD	

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
			
DMF No:			AADA:
Responsibilities:			
Profile:			OAI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-AUG-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: 1525864	FEI: 1525864	
	APTALIS PHARMA INC 845 CENTER DR VANDALIA, OH 45377		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	POWDERS (b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9615378 FEI: 3001027806

GILEAD ALBERTA ULC
1021 HAYTER RD NW

EDMONTON, , CANADA

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

(b) (4)

Profile:

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-JUN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: 2082946 FEI: 2082946

GILEAD SCIENCES INC
650 CLIFFSIDE DR

SAN DIMAS, CA 917732957

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE LABELER

Profile: POWDERS

(b) (4)

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-JUL-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 2952384 FEI: 1000523075

GILEAD SCIENCES INC
333 LAKESIDE DRIVE

FOSTER CITY, CA 944041147

DMF No:

AADA:

Responsibilities:

(b) (4)

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 21356/038
Orphan Code: 530
Priority: 1Y
Stamp Date: 16-JUN-2011
PDUFA Date: 18-JAN-2012
Action Goal:
District Goal:

Sponsor: GILEAD
333 LAKESIDE DR
FOSTER CITY, CA 94404
Brand Name: VIREAD(TENOFOVIR DISOPROXIL FUMARATE)300
Estab. Name:
Generic Name: TENOFOVIR DISOPROXIL FUMARATE
Product Number; Dosage Form; Ingredient; Strengths
001; TABLET; TENOFOVIR DISOPROXIL FUMARATE; 300MG

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	S. MILLER	Review Chemist	301-796-1418
	T. OLIVER	Team Leader	301-796-1728

Overall Recommendation:	ACCEPTABLE	on 12-JUL-2011	by M. STOCK	(HFD-320)	301-796-4753
	PENDING	on 11-JUL-2011	by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: (b) (4)
Responsibilities: (b) (4)
F: (b) (4)

AADA:

OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JUL-2011
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

/s/

NIKOO N MANOCHEHRI KALANTARI
01/25/2012