

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-356

CHEMISTRY REVIEW(S)

**REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)**

1. CHEMISTRY REVIEW #: 1

2. NDA #: 21-356

3. NAME & ADDRESS OF APPLICANT: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

4. SUPPLEMENT(S): N/A

5. PROPRIETARY NAME: VIREAD™

6. NONPROPRIETARY NAME: Tenofovir disoproxil fumarate (U.S.A.N. name)

7. CODE NAME/#: GS-4331-05; PMPA Prodrug (fumarate salt); bis-POC PMPA fumarate,
tenofovir DF

8. CHEM TYPE/SUBMISSION PRIORITY: 1 P

9. SUPPLEMENT(S) PROVIDE(S) FOR: N/A

10. RELATED DOCUMENTS

DOCUMENT DATE

CMC Issues (Teleconference)	7/2/01
CMC Comments & Recommendations (Telefacsimile)	7/3/01
CMC Comments & Recommendations (Telefacsimile)	7/20/01
Bottle and Carton Label Com. & Recom. (Telefacsimile)	8/20/01
Drug Substance & Drug Product Com. & Recom. (Telefacsimile)	8/28/01
Labeling Comments & Recom. (Telefacsimile)	10/10/01
Labeling and CMC Issues (Teleconference)	10/15/01

11. SUBMISSION(S) REVIEWED

DOCUMENT DATE

Original	4-30-01
Amendment 016	5-25-01
Amendment 036	7-6-01
Amendment 052	8-7-01
Amendment 054	8-13-01
Amendment 064	9-6-01
Amendment 072	9-20-01
Amendment 076	10-2-01
Amendment 079	10-16-01
Amendment 082	10-17-01

12. PHARMACOLOGICAL CATEGORY: Antiviral (HIV reverse transcriptase inhibitor)

13. Rx or OTC: Rx

14. DOSAGE FORM: Tablet

15. STRENGTH/POTENCY: 300 mg (Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil).

16. ROUTE OF ADMINISTRATION: Oral

17. SPOTS: No Yes

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

Name: 9-[(R)-2-
[[bis[[isopropoxycarbonyl]oxy]methoxy]phosphinyl]methoxy]propyl]a
denine fumarate (1:1) (IUPAC)
or
(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) (CAS)

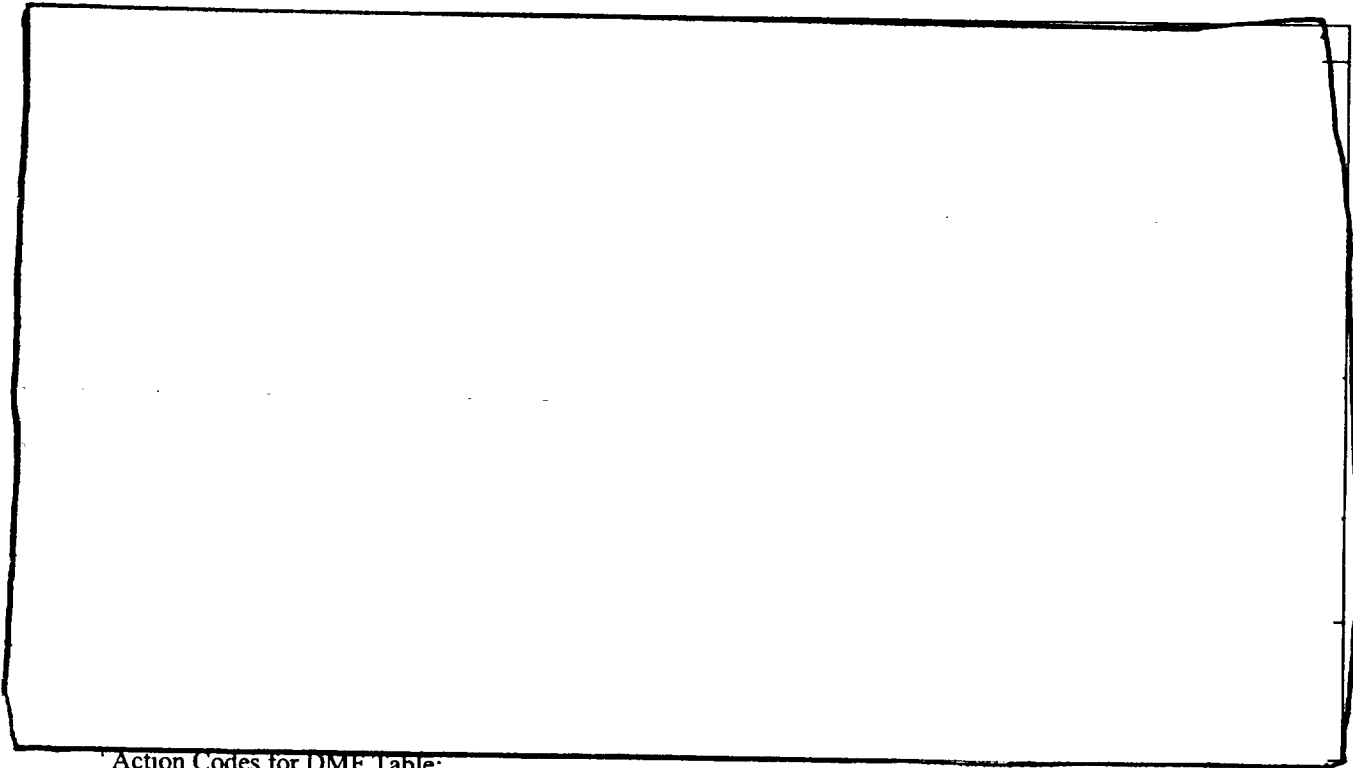
Molecular Formula: $C_{23}H_{34}N_5O_{14}P$
Molecular Weight: 635.32 (519.45 for free base)
Structure:



19. RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



Action Codes for DMF Table:

1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

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

20. STATUS OF CONSULTS AND OTHER REVIEWS

ITEM	RECOMMENDATION	RESONSIBILI TY	REVIEWER'S NAME
Microbiology	N/A	N/A	N/A
Inspection	Acceptable (10/18/01)	Establishment Evaluation	P. Lefler (HFD-324, DMPQ, OC)
Methods Validation	Pending	Analytical Methods Validation	Division of Pharmaceutical Analysis, St. Louis and Philadelphia District Laboratory
Biometrics	N/A	N/A	N/A
Biopharmaceutics	N/A	N/A	N/A
OPDRA	Trademark Acceptable	Trademark and	Jerry Phillips, R.Ph.,

	(7/23/01)	labels	OPDRA (HFD-400)
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21. REMARKS/COMMENTS:

Gilead Sciences, Inc. submitted this NDA for the approval of VIREAD™ (tenofovir disoproxil fumarate) tablets for the treatment of patients with HIV-1 infection. VIREAD™ is a fumaric acid salt of *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV reverse transcriptase. VIREAD™ tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The recommended dosing for adults is one 300 mg tablet once a day. The tablets are packaged in bottles of 30 count.

a) Drug Substance: Satisfactory

Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It is a high solubility drug according to the Biopharmaceutics Classification System. It has a single chiral center at the C-2 position of the propyl side-chain and it is manufactured as the *R*-enantiomer. It exists in two polymorphic forms.

According to the USP definition, it is sparingly soluble in water (pH 7.2, 12.1 mg/mL). It is non-hygroscopic.

The drug substance is manufactured at three facilities

The Applicant's initially proposed acceptance criteria, the FDA proposed criteria, and the final criteria are provided in the Drug Substance-Specifications section of the Review Notes. The revised specifications are acceptable. The batch analyses were provided for 54 lots (representing all commercial manufacturing sites) which included clinical, toxicology, development, and stability batches. Of these batches, 11 were made by the final commercial process. The results of the batch analyses for the primary batches indicated that the drug substance can be made with consistent quality and purity. The Reference Standard was well characterized and it was made by the proposed commercial manufacturing process.

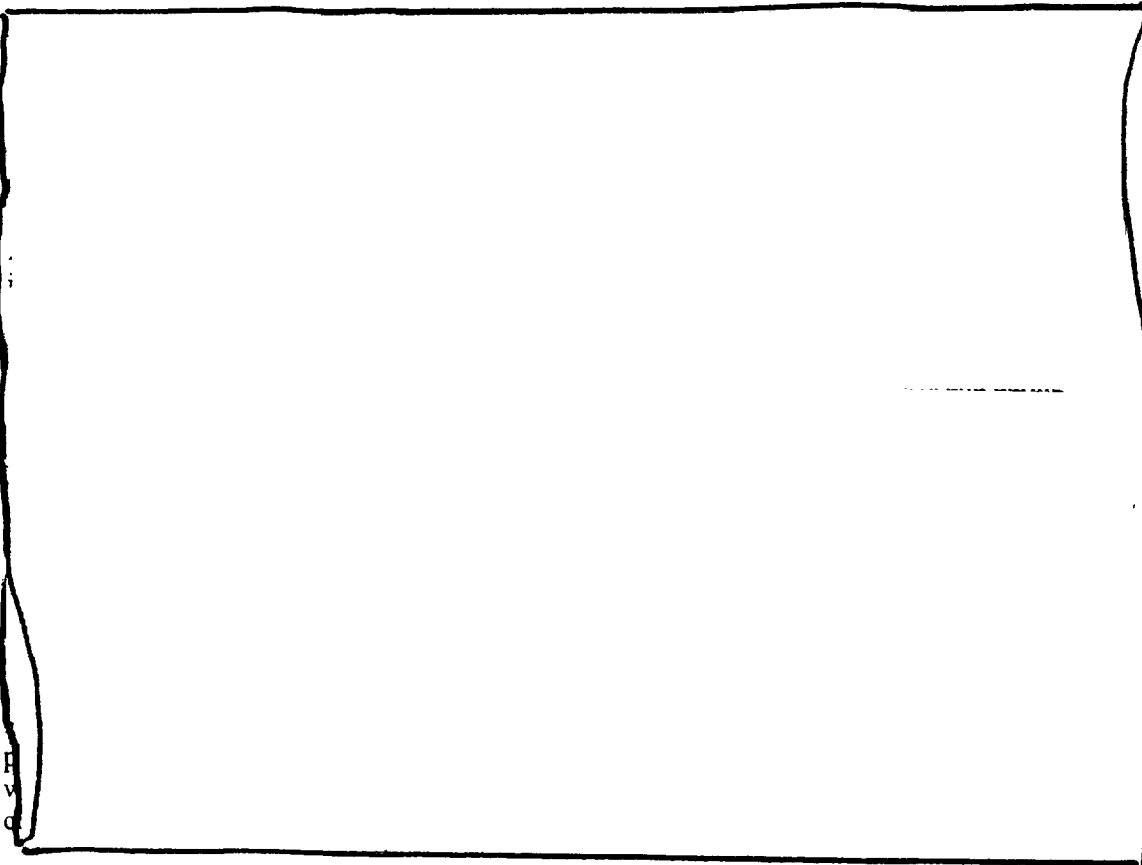
storage for 36 months under long-term conditions and by 1.7% upon storage for 6 months under accelerated conditions. The main degradant was [REDACTED] which increased by [REDACTED] after 36 months under long-term and by [REDACTED] after 6 months under accelerated conditions. The [REDACTED] impurity increased by [REDACTED] after 24 months under long-term and by [REDACTED] after 6 months under accelerated conditions. The [REDACTED] impurity did not increase much under long-term conditions but increased by [REDACTED] after 6 months under accelerated conditions. The remaining impurities did not increase much under either condition. All increases were within the range of the proposed limits. The drug substance was also demonstrated to be not photolabile. The Applicant proposed a retest period of 24 months when stored under refrigerated conditions (2-8°C) and it is acceptable.

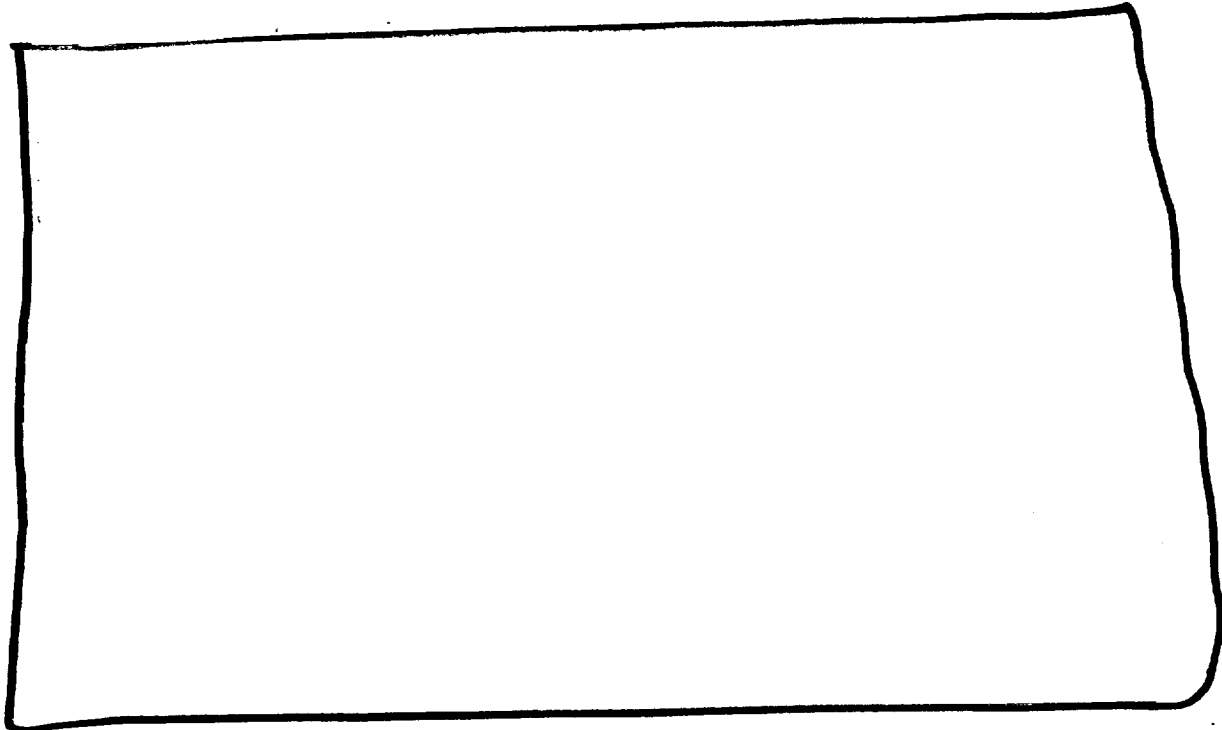
b) Drug Product: Satisfactory

VIREAD™ (tenofovir disoproxil fumarate) tablets, 300 mg are light blue, almond-shaped, film-coated with "GILEAD" and "4331" debossed on one side of the tablet and "300" debossed on the other side of the tablet. The dimensions of the tablet are 16.8 mm in length and 10.3 mm in width. The tablets are an immediate-release solid oral dosage form containing [REDACTED] tenofovir disoproxil fumarate (tenofovir DF). [REDACTED]

The components and composition and specifications for the excipients are acceptable. The tablets are manufactured at [REDACTED]

A. The manufacturing and packaging processes are clearly described and they are commonly used in the tablet manufacturing facilities.





c) Environmental Assessment: *Satisfactory*

The Applicant's justification for exemption from the environmental assessment requirement is acceptable.

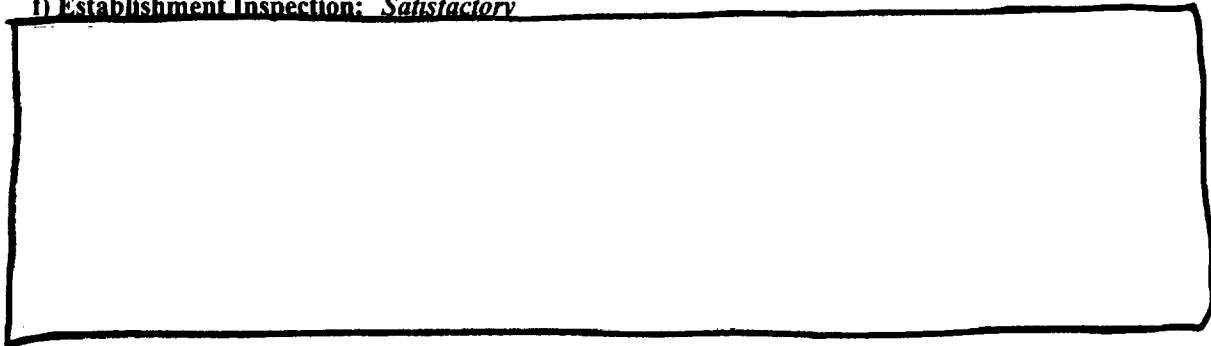
d) Methods Validation: *Pending*

The analytical methods validation by the Division of Pharmaceutical Analysis, St. Louis (HFD-920) and the Philadelphia District Laboratory is pending.

e) Labeling: *Satisfactory*

The CMC comments that are related to the initially submitted package insert, patient package insert, bottle label, and carton label were revised according to the mutual consent between the FDA and the Applicant. The final revised documents will be submitted by the Applicant by 10/26/01. The trademark "VIREAD™" for tenofovir disoproxil fumarate tablets, 300 mg, was reviewed by OPDRA and it was recommended as acceptable.

f) Establishment Inspection: *Satisfactory*



22. CONCLUSIONS & RECOMMENDATIONS:

From the CMC standpoint the NDA #21-356 for VIREAD™ (tenofovir disoproxil fumarate) tablets is recommended for approval. An expiration dating period of 24 months is recommended for VIREAD™ tablets that are packaged in bottles of 30 count and stored at 25°C (77° F). No Post-Marketing Commitments are necessary from the CMC perspective. In the NDA Action Letter, a statement should be included indicating that the analytical methods validation by the FDA District Laboratories is pending.

23. REVIEWER _____**DATE COMPLETED** 10-18-01

Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist

Concurrence:
HFD-530/SMiller

cc:

Orig. NDA #21-356
HFD-530/Chem TL/SMiller
HFD-530/MO/KStruble
HFD-530/Micro/NBattula

HFD-530/Chem/RKambhampati
HFD-830/Dir/CChen
HFD-530/PM/MHolloman
HFD-530/Pharm/PVerma

18-OCT-2001

FDA CDER EES

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ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21356/000	Priority: 1P	Org Code: 530
Stamp: 01-MAY-2001 Regulatory Due: 01-NOV-2001	Action Goal:	District Goal: 31-DEC-2001
Applicant: GILEAD 346 LAKESIDE DR FOSTER CITY, CA 94404	Brand Name: VIREAD(TENOFOVIR DISOPROXIL FUMARATE)300	
	Established Name:	
	Generic Name: TENOFOVIR DISOPROXIL FUMARATE	
	Dosage Form: TAB (TABLET)	
	Strength: 300 MG/TABLET	
FDA Contacts: M. HOLLOMAN (HFD-530)	301-827-2335	, Project Manager
R. KAMBHAMPATI (HFD-530)	301-827-2395	, Review Chemist
S. MILLER (HFD-530)	301-827-2392	, Team Leader

Overall Recommendation:

ACCEPTABLE on 18-OCT-2001 by P. LEFLER(HFD-324)301-827-0062

Establishment: 

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 01-OCT-2001
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

Responsibilities: 

Establishment: 2952384
 GILEAD SCIENCES INC
 346 LAKESIDE DR
 FOSTER CITY, CA 94404

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 18-OCT-2001
 Decision: -ACCEPTABLE
 Reason: BASED ON FILE REVIEW

Responsibilities: 

Establishment: 

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION

Responsibilities: 

18-OCT-2001

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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Milestone Date: 15-MAY-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:  DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: 

Establishment:  DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-MAY-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: 

Establishment:  DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-JUN-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: 

Establishment:  DMF No:
AADA No:

Profile: CSN OAI Status: NONE

Responsibilities: 

18-OCT-2001

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION



Establishment:



DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

