

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-356

ADMINISTRATIVE DOCUMENTS

Patent Information

1. Active Ingredient tenofovir disoproxil fumarate
2. Strength 300 mg
3. Trade Name VIREAD™ (submitted)
4. Dosage form and route of
administration tablet for oral administration
5. Applicant Name Gilead Sciences, Inc.
6. NDA Number 21-356 (filed under Section 505(b)(1) of the
Federal Food, Drug and Cosmetic Act)
7. First approval date Not yet approved*
8. Exclusivity: Pursuant to 21 CFR 314.108(b)(2), no person may
submit a 505(b)(2) application or ANDA for at
least 5 years from the date of approval of this
New Drug Application
9. Patent Information The following patents are listed in this NDA:
 - US Patent No. 4,808,716
 - US Patent No. 6,057,305
 - US Patent No. 5,922,695
 - US Patent No. 5,977,089
 - US Patent No. 6,043,230
 - US Patent No. 5,935,946

*Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial of financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

Patent Certification

Certification of the following patents are provided:

- US Patent No. 4,808,716
- US Patent No. 6,057,305
- US Patent No. 5,922,695
- US Patent No. 5,977,089
- US Patent No. 6,043,230
- US Patent No. 5,935,946

Attachment to Patent Information

First U.S. Patent Number: 4,808,716

Expiration Date: April 25, 2006

Coverage:

- | | | | | |
|---|-------------------------------------|---|--------------------------|---|
| 1. Drug substance (Active ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. Drug product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. Method of use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

Use For Which Approval Is Being Sought That Is Covered By Patent:

Therapy of HIV

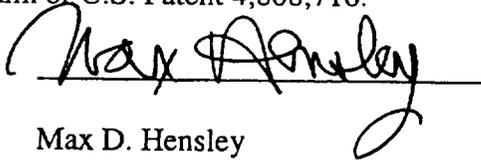
Name of Assignees of Record:

Rega Stichting, v.z.w. and Institute of Organic Chemistry and Biochemistry of the
Academy of Sciences of the Czech Republic

Declaration

The claims of U.S. Patent 4,808,716 in relevant part cover at least the compound PMPA, together with compositions containing same and uses thereof. PMPA is the parental drug released upon metabolism in vivo in humans of tenofovir disoproxil fumarate, the subject of the application for which approval is sought. Accordingly, the undersigned declares that making, using, selling, offering to sell or importing tenofovir disoproxil fumarate for the approved use would constitute at least contributory and/or induced infringement of at least one claim of U.S. Patent 4,808,716.

By:



Name: Max D. Hensley

Date:

4/11/01

Title: Vice President for Intellectual Property

Telephone

number: (650) 522-5878

Attachment to Patent Information

Second U.S. Patent Number: 6,057,305

Expiration Date: May 2, 2017

Coverage:

- | | | | | |
|---|-------------------------------------|---|-------------------------------------|---|
| 1. Drug substance (Active ingredient) | <input type="checkbox"/> | Y | <input checked="" type="checkbox"/> | N |
| 2. Drug product (Composition/Formulation) | <input type="checkbox"/> | Y | <input checked="" type="checkbox"/> | N |
| 3. Method of use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

Use For Which Approval Is Being Sought That Is Covered By Patent:

Therapy of HIV

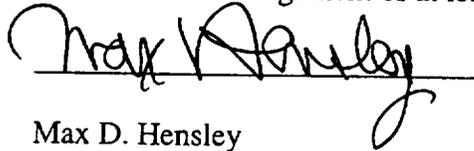
Name of Assignees of Record:

Rega Stichting, v.z.w. and Institute of Organic Chemistry and Biochemistry of the
Academy of Sciences of the Czech Republic

Declaration

The claims of U.S. Patent 6,057,305 in relevant part cover at least the use of (R)-PMPA substantially free of (S)-PMPA for the treatment of human immunodeficiency virus. (R)-PMPA is the parental drug released upon metabolism in vivo in humans of tenofovir disoproxil fumarate, the subject of the application for which approval is sought. Accordingly, the undersigned declares that making, using, selling, offering to sell or importing tenofovir disoproxil fumarate for the approved use would constitute at least contributory and/or induced infringement of at least one claim of U.S. Patent 6,057,305.

By:



Name:

Max D. Hensley

Date:

4/11/01

Title:

Vice President for Intellectual Property

Telephone

number: (650) 522-5878

Attachment to Patent Information

Third U.S. Patent Number: 5,922,695

Expiration Date: July 25, 2017

Coverage:

- | | | | | |
|---|-------------------------------------|---|--------------------------|---|
| 1. Drug substance (Active ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. Drug product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. Method of use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

Use For Which Approval Is Being Sought That Is Covered By Patent:

Therapy of HIV

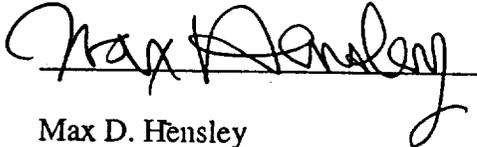
Name of Patent Owner:

Gilead Sciences, Inc.

Declaration

The undersigned declares that making, using, selling, offering to sell or importing tenofovir disoproxil fumarate for the approved use would constitute infringement of at least one claim of U.S. Patent 5,922,695.

By:



Name:

Max D. Hensley

Date:

4/11/01

Title:

Vice President for Intellectual Property

Telephone

number: (650) 522-5878

Attachment to Patent Information

Fourth U.S. Patent Number: 5,977,089

Expiration Date: July 25, 2017

Coverage:

- | | | | | |
|---|-------------------------------------|---|--------------------------|---|
| 1. Drug substance (Active ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. Drug product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. Method of use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

Use For Which Approval Is Being Sought That Is Covered By Patent:

Therapy of HIV

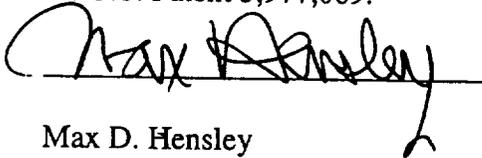
Name of Patent Owner:

Gilead Sciences, Inc.

Declaration

The undersigned declares that making, using, selling, offering to sell or importing tenofovir disoproxil fumarate for the approved use would constitute infringement of at least one claim of U.S. Patent 5,977,089.

By:



Name:

Max D. Hensley

Date:

4/11/01

Title:

Vice President for Intellectual Property

Telephone

number:

(650) 522-5878

Attachment to Patent Information

Fifth U.S. Patent Number: 6,043,230

Expiration Date: July 25, 2017

Coverage:

- | | | | | |
|---|-------------------------------------|---|-------------------------------------|---|
| 1. Drug substance (Active ingredient) | <input type="checkbox"/> | Y | <input checked="" type="checkbox"/> | N |
| 2. Drug product (Composition/Formulation) | <input type="checkbox"/> | Y | <input checked="" type="checkbox"/> | N |
| 3. Method of use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

Use For Which Approval Is Being Sought That Is Covered By Patent:

Therapy of HIV

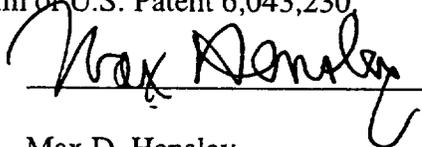
Name of Patent Owner:

Gilead Sciences, Inc.

Declaration

The undersigned declares that making, using, selling, offering to sell or importing tenofovir disoproxil fumarate for the approved use would constitute infringement of at least one claim of U.S. Patent 6,043,230.

By:



Name:

Max D. Hensley

Date:

4/01

Title:

Vice President for Intellectual Property

Telephone

number: (650) 522-5878

Attachment to Patent Information

Sixth U.S. Patent Number: 5,935,946

Expiration Date: July 25, 2017

Coverage:

- | | | | | |
|---|-------------------------------------|---|--------------------------|---|
| 1. Drug substance (Active ingredient) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. Drug product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. Method of use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |

Use For Which Approval Is Being Sought That Is Covered By Patent:

Therapy of HIV

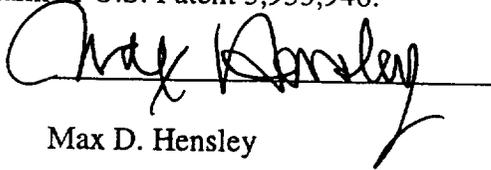
Name of Patent Owner:

Gilead Sciences, Inc.

Declaration

The undersigned declares that making, using, selling, offering to sell or importing tenofovir disoproxil fumarate for the approved use would constitute infringement of at least one claim of U.S. Patent 5,935,946.

By:



Name: Max D. Hensley

Date: 4/11/01

Title: Vice President for Intellectual Property

Telephone
number: (650) 522-5878

EXCLUSIVITY SUMMARY for NDA # 21-356 SUPPL # _____

Trade Name VIREADTM Generic Name TENOFOVIR DF

Applicant Name GILEAD SCIENCES HFD- 530

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____
Investigation #__, Study # _____
Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2
IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

If yes, explain: _____

 /S/

Signature of Preparer
Title: RHPM

10-26-01

Date

 /S/

 /S/ _____
Signature of Office or Division Director

10-26-01

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

N/A Date of Written Request from FDA 1/1. Application Written Request was made to: NDA/IND#
 Timeframe Noted in Written Request for Submission of Studies 1/1.
 NDA# 21356 Supplement # Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
 Sponsor GILEAD SCIENCES
 Generic Name TENOFOVIR DF Trade Name VIREAD
 Strength 300 mgx Dosage Form/Route TABLET
 Date of Submission of Reports of Studies 1/1. N/A
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 1/1.

Was a formal Written Request made for the pediatric studies submitted?	Y <u> </u>	N/A N/A N/A N/A
Were the studies submitted after the Written Request?	Y <u> </u>	
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <u> </u>	
Was the timeframe noted in the Written Request for submission of studies met?	Y <u> </u>	
If there was a written agreement, were the studies conducted according to the written agreement? <div style="text-align: center;">OR</div> If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <u> </u>	
Were the studies responsive to the terms of the Written Request?	Y <u> </u>	

NOTE: WRITTEN REQUEST PROPOSAL IN-HOUSE
 FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-104.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **Granted** **Denied**

Existing Patent or Exclusivity Protection:

<u>NDA/Product #</u>	<u>Eligible Patents/Exclusivity</u>	<u>Current Expiration Date</u>
_____	_____	_____
_____	_____	_____
_____	_____	_____

SIGNED _____ DATE _____

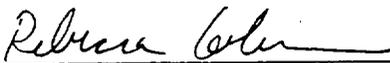
cc:
 Archival NDA/IND ##-###
 HFD-xxx/division file
 HFD-xxx/PM-CSO

 HFD-93/Division of Data Management Services
 HFD-600/Office of Generic Drugs
 HFD-2/MLumpkin
 HFD-104/DMurphy
 HFD-104/Crescenzi

DEFERRED UNTIL
 11/01/2004
 (SEE APPROVAL LETTER)

Debarment Statement

Neither Gilead Sciences, Inc. nor any of its contract operations, laboratories or individuals involved in the development or submission of records or data regarding tenofovir disoproxil fumarate has used and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 3069 (a) or (b)] or the Generic Drug Enforcement Act of 1992 (21 U.S.C. 335a(k)(1)).



Rebecca L. Coleman, PharmD
Director, Regulatory Affairs

4/26/01

Date

**DIVISION DIRECTOR (ACTING)
SUMMARY REVIEW**

Date: October 22, 2001

From: Debra Birnkrant, M.D.
Acting Director, Division of Antiviral Drug Products(DAVDP)

To: Division File

Subject: Division Director's Concurrence with the Accelerated Approval of
Tenofovir DF, NDA 21-356

I am in agreement with the conclusions reached by Dr. Struble in her review of NDA 21-356 for Tenofovir DF for the treatment of HIV-1 infection in adults. Her conclusions support the accelerated approval of Tenofovir DF and are based on results of three supportive and two pivotal studies as well as the conclusions reached by the nonclinical, clinical biopharmaceutics and biometrics reviewers.

After reviewing the NDA package, I would like to comment on the following areas that were also presented to the Division of Antiviral Drug Products' advisory committee on October 3, 2001: 1) endpoint for the clinical trials, 2) indications and usage section of the label, 3) bone and renal toxicity issues and 4) resistance data.

1. Endpoint for Clinical Trials

The primary endpoint chosen for trials 902 and 907 was the $DAVG_{24}$ defined as the time-weighted average between the first post-baseline value through the last available value up to week 24 minus the baseline value. This endpoint was chosen based on the designs of the studies, i.e. an intensification design where only one drug was added to background therapy and the patient population, i.e. treatment experienced. It was felt that this endpoint would be the best viral load metric to discriminate between the treatment effects of Tenofovir DF and placebo whereas other endpoints, such as proportion below the limit of quantification of the HIV RNA assays that are used in clinical trials of naïve patients would not be as sensitive in populations that are unlikely to maximally suppress virus. The use of this endpoint was also detailed in our guidance document on the clinical considerations for accelerated and traditional approval of antiretroviral drugs using plasma HIV RNA measurements and discussed at an advisory committee meeting on the development of drugs for treatment experienced patients held in January 2001. Secondary endpoints in trials 902 and 907 included mean change from baseline and percent or proportion below the limit of quantification of the HIV RNA assays; all endpoints appear in the label to give a full picture of the activity of Tenofovir df in treatment experienced populations.

2. Indications and Usage Section of the Label

Pivotal trials, 902 and 907 were of similar design and conducted in a treatment experienced population that had a significant percentage of mutations to all three classes of approved antiretroviral agents. Although the applicant demonstrated safety and efficacy in this treatment experienced population, the indications and usage section of the label will broadly state that the drug should be used in combination with other antiretroviral drugs in the treatment of HIV infected adults. To provide balance to this statement, this section will, however, contain statements to inform prescribers and patients that data from a naïve population was not contained in the NDA package and therefore a risk/ benefit statement regarding this population can not be made at this time. In addition this section will contain the following statements:

- There are no study results demonstrating the effect of tenofovir on clinical progression of HIV.
- The use of VIREAD should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history

Of note, Gilead is conducting study 903 in a naïve population and this study will be part of a traditional approval package along with a second confirmatory study.

3. Bone and Renal Toxicity Issues

Bone mineral density abnormalities and/or osteomalacia were found in three species in nonclinical studies. Only limited data related to bone metabolism were collected in studies 902 and 907. Based on the limited clinical data, which included an assessment of fracture rates in the clinical trials, there was no evidence that Tenofovir DF caused bone abnormalities to the extent seen in the nonclinical studies. This subject was also brought before experts on our advisory committee who recommended patient monitoring for signs of osteomalacia in those subjects who may be at risk.

In addition, the applicant will be asked to investigate bone toxicity as part of their phase 4 commitments. Specifically, the applicant will be required to submit complete analyses of the safety data with respect to bone effects from studies 903 and 928. The final study reports should include detailed analyses of the BMD results and the laboratory parameters specific to bone metabolism, including, but not limited to, osteocalcin, bALP, N and C- teleopeptide, vitamin D and PTH. The final study reports for studies 903 and 928, a second confirmatory in treatment experienced pediatric patients, should include analyses for these parameters through week 96 and 48, respectively. Long term safety monitoring for serious adverse events and fractures from study 910, including BMD changes in patients participating in the BMD substudy should also be submitted; this study will follow approximately 575 patients for 4 years.

Similar to bone toxicity, renal toxicity was also seen in nonclinical testing. During clinical testing, however, clinically significant renal events were infrequent. As both toxicities may more likely be seen with long term use of Tenofovir DF, they will continue to be assessed in the aforementioned studies. Wording will appear in the label to state that if bone or renal abnormalities are suspected based on routine monitoring, additional testing may be appropriate.

4. Resistance data

There were more resistance data in this NDA than any other NDA reviewed by DAVDP, although there were a limited number of patients for some primary nucleoside reverse transcriptase inhibitor(NRTI) and multidrug resistant mutations to be able to make definitive conclusions. In sum, the genotype and phenotype data suggested the following:

- The presence of M41L or L210W was associated with diminished Tenofovir DF efficacy.
- Tenofovir DF efficacy is reduced in patients with ≥ 3 thymidine analogue mutations that included M41L or L210W.
- Viruses expressing the K65R mutation showed reduced susceptibility to Tenofovir DF in vitro; all 6 patients expressing this mutation at baseline did not respond to Tenofovir DF.
- Cross-resistance was not observed between Tenofovir DF and the lamivudine/abacavir associated mutation, M184V.
- Phenotypic analyses showed reduced response rates at > 4 -fold reduced susceptibility to Tenofovir DF.

The applicant will be requested to characterize the role of the K65 R mutation in conferring resistance to Tenofovir DF and cross resistance between Tenofovir DF and other NRTIs, specifically didanosine and abacavir as part of their phase 4 commitments.

In conclusion, adequate data have been presented to determine that Tenofovir DF is safe and effective for the treatment of HIV infected adults greater than 18 years of age. The applicant will be conducting additional studies to support the traditional approval of Tenofovir DF, including studies in a naïve patient population and a treatment experienced pediatric population. The applicant will be required to conduct, complete and submit their phase 4 commitments according to the specifics outlined in the approval letter. Lastly, the applicant should be commended for conducting clinical trials in a patient population with limited treatment options. In this way, the applicant has fulfilled the spirit of the accelerated approval regulations.

**MEDICAL GROUP LEADER
SUMMARY REVIEW**

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 10-19-01

FROM: Jeffrey S. Murray M.D., M.P.H.
Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-356, Tenofovir DF for the Treatment of HIV Infection

1. Background

VIREAD is the trade name for tenofovir DF (disoproxil fumarate), which is a pro-drug of tenofovir. Tenofovir is an adenine nucleoside monophosphate analogue with activity against HIV reverse transcriptase. Unlike previously approved nucleoside analogue drugs, tenofovir contains an initial phosphate group. Nevertheless, the Division considers tenofovir to be a member of the class of drugs referred to as NRTI (nucleoside reverse transcriptase inhibitors) as it has structural similarity and the same mechanism of action of these drugs. As such, it is possible that tenofovir may share similar clinical characteristics or exhibit cross-resistance with NRTIs. In fact, analyses of clinical resistance data show that certain NRTI-selected mutations may confer cross-resistance to tenofovir.

For the remainder of this memo, VIREAD (tenofovir DF) will be referred to as simply tenofovir. In this NDA, Gilead Sciences requested an accelerated approval and priority review of tenofovir. The Division concurred that a priority review and consideration for an accelerated approval was justified, because Gilead had studied tenofovir in treatment experienced patients with continued replication of HIV. The majority of these patients harbored isolates with mutational patterns suggesting reduced susceptibility to many of the approved NRTIs. Thus, tenofovir has the potential to be useful in patients who have exhausted available treatment options. This fulfills one of the regulatory criteria of subpart H.

For detailed analyses and displays of safety and efficacy data, the reader should refer to reviews prepared by Kimberly Struble, Pharm.D. (Senior Regulatory Review Officer) and Rafia Bhore Ph.D. (Biometrics)

2. Summary of Efficacy

The efficacy of tenofovir was demonstrated in two randomized, placebo-controlled trials (902 and 907). In both studies treatment experienced patients with continued HIV replication were randomized to receive tenofovir or placebo. Mean HIV RNA decreases among patients randomized to tenofovir were similar in both studies and approximated 0.5- to 0.6- \log_{10} copies/mL over a 24-week time period. Decreases in HIV RNA of this magnitude have previously been shown to correlate with clinical benefit. The Division considers evaluations of mean changes in HIV RNA as an acceptable primary endpoint for patient populations in which a relatively small proportion of patients are expected to achieve HIV RNA levels below an assay limit.

The magnitude of HIV RNA reduction among patients randomized to tenofovir is noteworthy, considering that these patients had been treated extensively with NRTIs (mean duration approximating 5 years).

The applicant also evaluated the proportion of patients who achieved < 400 and < 50 copies/mL of HIV RNA, the assay limit of the standard and ultrasensitive Roche Monitor Assays, respectively. In both studies, a larger proportion of patients randomized to tenofovir, as compared to placebo, achieved levels below the assay limits. This was statistically significant for the larger study (#907).

In study 907, modest but statistically significant increases in CD4 cell counts occurred among patients randomized to tenofovir. The net treatment effect (time-averaged) for CD4 cell counts was a gain of approximately 20 cells. For study 902, there were no statistically significant differences with respect to changes in CD4 cell counts between patients randomized to tenofovir 300 mg and those randomized to placebo. However, study #902 was a much smaller study than study #907, and CD4 cell count changes among the doses evaluated (75 mg, 150 mg, 300 mg) in study 902 were widely variable. In addition, in both studies, tenofovir 300 mg was added as a single agent to patients with relatively high and stable CD4 cell counts. The trial design may have limited the ability to demonstrate larger effects on CD4 cell counts. Overall, the modest changes observed for CD4 cell counts do not call into question the validity of the virologic results, the primary endpoint.

3. Summary of Clinical Virology Data

This NDA contained more clinical resistance data than any previous NDA for an antiretroviral drug. For a detailed review of the clinical resistance data, refer to the review prepared by Dr. Struble. Although tenofovir reduced HIV RNA levels in a population of patients with prolonged prior NRTI therapy, the presence of certain NRTI-associated mutations diminished the antiviral effect. In analyses performed by FDA and the applicant, thymidine analogue associated mutations (TAMS) at positions 210 and/or 41 reduced the activity of tenofovir. Consequently, prior treatment with zidovudine or stavudine may confer some degree of cross-resistance to tenofovir. The activity of tenofovir did not appear to be negatively affected by the presence of the lamivudine/abacavir-associated mutation (M184V). Relatively few individuals had the didanosine-associated mutation (L74V/I) at baseline; however, virologic response appeared to be reduced in this subset as compared to patients without this mutation at baseline. This may have been confounded by the presence of additional mutations.

Baseline phenotype also predicted subsequent virologic response to tenofovir. Reduction in HIV RNA appeared to be largely diminished when baseline susceptibility was reduced by four-fold or greater.

4. Summary of Safety

With respect to clinical adverse events of at least moderate intensity, tenofovir and placebo appeared to be similarly tolerated. However, when assessing all severity grades (including those judged to be mild) the percentage of patients experiencing some gastrointestinal events, specifically vomiting and flatulence, appeared somewhat higher among those randomized to tenofovir compared to placebo. In the principal studies in the NDA, there were no apparent differences between tenofovir and placebo with respect to laboratory abnormalities.

During the development of tenofovir, the Division requested that the sponsor monitor clinical trial participants for the occurrence of renal or bone-related adverse events because bone and kidney were target organs of toxicity in animal toxicology studies. Bone toxicity in animals included decreases in bone mineral density and osteomalacia. Discontinuation of drug or reduction of dose appeared to ameliorate the bone toxicity observed in monkeys in one study. Abnormalities in phosphate metabolism were also observed to varying degrees among the animal species tested and may have been associated with bone toxicity. However, at this time, the mechanism of bone toxicity has not been defined.

In the NDA safety database there was no evidence that tenofovir caused bone toxicity among patients receiving tenofovir. No patient had symptoms and signs suggestive of osteomalacia.

Documented fractures appeared to be related to traumatic injury and did not have delayed or abnormal healing. No significant or consistent changes were observed in a subset of patients who underwent bone mineral density evaluations by . Tenofovir did not appear to affect serum phosphate, calcium or creatinine levels.

In short, the proposed human dose (300 mg/day) produces tenofovir concentrations within the range of the no effect level for bone and renal toxicity in all animal species tested. Therefore, there appears to be a clinical margin of safety for bone and kidney toxicity. In addition signs and symptoms of tenofovir-related bone and/or renal abnormalities were not detected in studies in humans. It is not known whether subtle effects on bone or kidney will become clinically apparent with long-term use of tenofovir.

5. Summary of Regulatory Issues

Although the Division was confident that the applicant had demonstrated safety and efficacy of tenofovir in the population studied, the Division of Antiviral Drug Products advisory committee convened on Oct. 3, 2001 to discuss four issues relating to the tenofovir application. The Division asked the committee to comment on the proposed treatment indication, the relevance of the clinical resistance analyses, the assessment of the toxicology and safety data relating to bone abnormalities, and the applicant's plans for traditional approval and phase 4 studies. These issues are discussed below.

1. Indication:

The discussion relating to indication revolved around restricting the indication to treatment experienced patients versus allowing a broad indication for HIV infection. The committee was divided in their recommendations regarding the breadth of the treatment indication that would be most appropriate for tenofovir. Some committee members believed that it would be biologically implausible for the activity of tenofovir to be smaller in treatment naïve patients than what had been observed in treatment-experienced patients. However, they acknowledged that studies in treatment naïve individuals are ongoing and data are not yet available. Therefore some committee members concluded that the risk-benefit ratio for treatment naïve patients had not yet been established. Some members had concerns regarding potential risks in treatment naïve patients given the bone abnormalities observed in animal studies (see summary of safety, above, and item #2, below).

Although not specifically discussed during the advisory committee meeting, one may consider that a growing proportion of treatment naïve individuals may be harboring resistant HIV, as a result of the well-documented rise in transmission of resistant strains of HIV. Therefore the distinction between treatment naïve and treatment experienced individuals may be diminishing. In the future, drug susceptibility testing may gain further importance in choosing drugs for treatment naïve individuals.

In addition, there may be subgroups of treatment naïve patients, for which tenofovir's tolerability profile and ease of administration (one tablet once a day) would provide a tangible advantage over existing treatment options. With this in mind, some committee members were concerned about the potential ramifications of a restrictive indication on third-party reimbursement.

Taking all these points into careful consideration, the Division decided to grant an HIV treatment indication that is similar to that of all of the other antiretrovirals. However, this indication is followed by caveats regarding usage. This approach is similar to that used in recent revisions of the amprenavir and delavirdine labels, in which a broader indication is later qualified by statements regarding the limitations of the supporting data. In the tenofovir label the indication and usage section will have the following statements.

VIREAD™ is indicated in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from two controlled studies in treatment experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Studies in antiretroviral naïve patients are ongoing; consequently, the risk-benefit ratio for this population has yet to be determined.

Additional important information regarding the use of VIREAD for the treatment of HIV infection:

- There are no study results demonstrating the effect of VIREAD on clinical progression of HIV.
- The use of VIREAD should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history (See Microbiology section: Clinical Studies – Antiviral activity of VIREAD in patients with previous antiretroviral therapy).

The review team believes that the wording of the indication appropriately reflects the limitations of the data and the concerns of the advisory committee.

2. Bone Toxicity:

Although the committee and Division concurred that clinical signals of bone toxicity have not yet surfaced, all agreed that continued monitoring for this toxicity is needed. This will be accomplished, primarily, in ongoing study #903, which will follow treatment naïve patients receiving either tenofovir or stavudine (in combination with lamivudine and efavirenz) for two years. Bone biomarkers and bone densitometry will be monitored in all study participants. The committee guest endocrinologists concurred with the plans that Gilead set forth for assessing potential bone toxicity in clinical trials. However, the committee strongly encouraged the applicant to conduct more studies to characterize the mechanism for bone toxicity. Delineation of the mechanism could provide important information for monitoring, preventing, or treatment of potential bone toxicities.

3. Clinical Resistance Data:

Overall, the committee was favorably impressed with the amount and scope of the resistance data and analyses presented. They acknowledged limitations of the clinical resistance analyses resulting from the large number of mutations and combinations of mutations possible in treatment experienced patients. The multiplicity of potential comparisons limits the ability to conduct testing for statistical significance. In addition, because one cannot fully predict a new drug's resistance pattern when designing a protocol, it is impossible to predefine all clinical resistance analyses that may be of interest. Despite these caveats, committee members with expertise in this area strongly recommended inclusion of the descriptive information correlating baseline genotype/phenotype with virologic response. They believed the data were convincing and would be useful information for the practicing HIV physician.

4. Traditional Approval Plans/Phase 4

In addition to the phase 3 study in treatment naïve patients (study 903), Gilead has proposed a second confirmatory study to be conducted in treatment experienced children. This would allow for more information regarding the performance of tenofovir in treatment-experienced patients with higher viral loads. With close monitoring of markers for potential bone toxicity, the committee was in agreement with commencing studies in children. It should be noted that studies in children had been delayed initially pending bone safety information in adults. The safety data from this application provide some reassurance that marked bone toxicity is

unlikely to occur over 24-48 weeks with 300 mg of tenofovir. Therefore, it is appropriate at this time to conduct studies in children in need of new therapeutic options.

Pharmacokinetic/safety studies will precede the planned confirmatory efficacy study.

The committee also strongly encouraged the completion of a pharmacokinetic study in individuals with renal impairment as soon as possible. Other suggested studies were those evaluating potential drug interactions with similarly excreted drugs. Additional interaction studies with other antiretroviral drugs were also suggested. (See the review prepared by Jooran Kim, Pharm.D, Clinical Pharmacology, for further details)

6. Risk Communications

At this time, there is no need for additional communication of risk beyond what will be highlighted in the package insert. The tenofovir package insert will carry the same box warning as that for all other NRTI. It is a class warning describing the occurrence of lactic acidosis and hepatic steatosis associated with the use of nucleoside analogues. This class warning was included because the Division believes that tenofovir is a member of the NRTI class. The applicant should conduct further studies evaluating this potential toxicity, should they seek to have the box warning removed.

In addition the insert will also include a Warning recommending that tenofovir not be used in patients with renal impairment (defined as a creatinine clearance < 60 mL/min). A pharmacokinetic study should be forthcoming. At the time of review a protocol was in the last stages of development.

The potential for bone toxicity is discussed under the Precautions section of the label. Further information gathered in ongoing and planned investigations, as part of the applicant's phase 4 commitments, will be used for future revisions to the label.

7. Conclusions

I concur with the clinical review prepared by Kimberly Struble, Pharm.D. Gilead has adequately demonstrated that tenofovir is safe and effective in the treatment of HIV infection. This new antiretroviral may offer therapeutic benefit for patients in need of new treatment options. Accelerated approval of tenofovir should be granted.

**APPEARS THIS WAY
ON ORIGINAL**

EXTERNAL CONSTITUENT PARTICIPANTS AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Raymond Bendele, DVM, PhD	Vice President, Life Sciences	Gilead Sciences, Inc
2. Norbert Bischofberger, PhD	Executive Vice President, Research and Development	Gilead Sciences, Inc
3. Carol Brosgart, MD	Vice President, Clinical Research	Gilead Sciences, Inc
4. Andrew Cheng, MD, PhD	Associate Director, Clinical Research	Gilead Sciences, Inc
5. Rebecca Coleman, Pharm D	Director, Regulatory Affairs	Gilead Sciences, Inc
6. Dennis Meyer, DVM	Clinical Pathology	Gilead Sciences, Inc
7. Michael Miller, PhD	Director, Clinical Pathology	Gilead Sciences, Inc
8. Alan S. Taylor, PhD	Vice President, Regulatory Affairs	Gilead Sciences, Inc
9. Jay Toole, MD, PhD	Vice President, Clinical Research	Gilead Sciences, Inc

BACKGROUND:

Reference is made to [redacted] submitted March 19, 1997; an End-of-Phase-2 Meeting on October 22, 1999 and the official minutes of that meeting; a teleconference on December 13, 1999; and numerous, related facsimile and electronic mail communications (emails) between DAVDP and Gilead Sciences between October 22, 1999 and September 6, 2000.

Reference is also made to a facsimile dated October 17, 2000 containing RRO review comments SN-121 and SN-123; an approval letter dated November 7, 2000 granting fast track designation to tenofovir; a letter dated November 27, 2000 summarizing DAVDP's comments regarding Gilead's proposed development plans and NDA submission of tenofovir DF; a facsimile dated December 13, 2000 containing RRO review comments on the Expanded Access Program (EAP) Protocol (GS-00-955) SN-142; an email dated December 13, 2000 requesting further information about fracture search methodology; three teleconferences held January 18, January 19, and January 22, 2001 to discuss bone fracture and adverse event reporting; a facsimile dated February 20, 2001 requesting adverse event and RNA/CD4 datasets; a teleconference held March 19, 2001 to discuss pre-NDA meeting materials and details about submission of the tenofovir NDA; SN-186 dated March 21, 2001 containing pre-NDA meeting materials; a facsimile dated March 30, 2001 containing RRO review comments on protocol 903 SN-178; a facsimile dated March 30, 2001 requesting datasets; an email with attachment dated April 19, 2001 containing virology genotype datasets for Studies 902 and 907; an email with attachment dated April 19, 2001 containing Gilead's slides and agenda for the pre-NDA meeting presentation; and to numerous facsimile and email communications between DAVDP and Gilead Sciences between September 7, 2000 and April 20, 2001.

Reference is also made to a pre-NDA meeting on April 20, 2001 and the official minutes of that meeting to discuss clinical issues; to the submission of NDA 21-356 for tenofovir DF dated April 30, 2001 and received May 1, 2001; a facsimile dated May 9, 2001 approving Gilead's Serious Adverse Event Reporting Plan for notification of investigators in the Expanded Access Protocol (EAP); a facsimile dated May 14, 2001 requesting that Gilead submit a pediatric protocol; a facsimile dated May

16, 2001 approving Gilead's EAP SN-203; a facsimile dated June 14, 2001 approving changes to the EAP SN-215; a facsimile containing RRO review comments about the collection of lactate levels in protocol 903 SN-178; a teleconference held August 08, 2001 to discuss the pediatric expanded access protocol and collection of pharmacokinetic (PK), dosing, and safety data; and to numerous facsimile and email communications between DAVDP and Gilead Sciences between April 21, 2001 and August 10, 2001.

Please see APPENDIX A for more information on the studies discussed in this document.

MEETING OBJECTIVES:

This NDA meeting between representatives of Gilead Sciences, Inc and DAVDP was held to discuss clinical issues related to the submission of NDA 21-356 for Tenofovir DF (*VIREAD*).

DISCUSSION POINTS:

1. PRE-CLINICAL DATA ON BONE EFFECTS:

The Division stated that a definitive conclusion regarding tenofovir's lack of a direct effect on bone could not be made at this time. However, Gilead believes there is no evidence that tenofovir has a direct effect on bone. The supporting data, summarized below, was reviewed during the meeting.

- No toxicity to human fetal osteoblasts in vitro
- No abnormal bone development in monkey fetuses exposed to high plasma levels in utero
- No abnormal bone development in newborn rats and rabbits exposed in utero in reproductive toxicology studies
- Bone effects are secondary to negative phosphate balance, specifically due to a reduced intestinal absorption and/or increased urinary excretion.

Gilead reviewed the mechanisms of the phosphate effects which included sodium phosphate (NaPi) cotransporter protein studies. Gilead concluded that results from this study suggest that tenofovir interacts with NaPi cotransporter proteins, thereby inhibiting phosphate absorption and/or renal phosphate reabsorption.

Data regarding NaPi cotransporters had not been previously submitted to the Division. It was agreed that Gilead would submit this study report and also provide a document summarizing the nonclinical bone evaluation. A subsequent teleconference will be scheduled to discuss this information.

2. CONCLUSIONS REACHED REGARDING THE CLINICAL DATA ON BONE EFFECTS:

- Because there is no data on the long-term effects of TNV in humans, Gilead has agreed to the following long-term safety evaluation plans:

- ✦ Study 910 will follow approximately 600 patients (rollovers from Studies 901, 902, and 907) through a common closing date of December 1, 2002. This allows capture of over four years of follow-up;
- ✦ Clinical chemistries (collection of serum sodium, potassium, chloride, bicarbonate creatinine, BUN, glucose, calcium, phosphorus, magnesium, total alkaline phosphatase, total bilirubin, AST, ALT, and amylase) and monitoring for bone fracture events will be included in the follow-up for study 910.
- ✦ Patients originally enrolled in study 902 will continue to have Vitamin D and PTH measured every 24 weeks. In study 907, no bone specific bio-markers were collected.
- The Division will seek the Antiviral Advisory Committee's (AVAC) assessment regarding the preclinical and clinical data on bone abnormalities. In addition the advisory committee may be asked to comment on the long term follow up plan for monitoring bone abnormalities.

3. *VIREAD* INDICATION:

- Gilead's proposal: "TNV DF, in combination with other antiretroviral agents, is indicated for the treatment of HIV-infected in adults."
- The Division plans to solicit the committee's advise regarding what patient population should tenofovir treatment be recommended.

4. CROSS-RESISTANCE (MICROBIOLOGY):

Gilead reviewed results from the genotypic analyses of specific thymidine analog mutations (TAMs). There was general agreement between the FDA and Gilead results for these analyses. These analyses show that the activity of tenofovir appeared to be diminished in patients expressing the M41L, L210W or T215Y/F mutation compared to patients who did not have these mutations at baseline. Gilead pointed out that although this analysis showed a diminished response in tenofovir treated patients expressing the T215Y/F mutation at baseline it was found that this mutation did not affect tenofovir efficacy. In fact the diminished response noted in patients expressing the T215Y/F mutation at baseline appears to be due to the presence of the M41L or L210W mutation and not the T215Y/F mutation. Gilead concluded that the number and type of TAMs affect tenofovir efficacy. Patients with ≥ 3 TAMs including M41L or L210W at baseline had reduced response rates. The Division will confirm the results of this analysis. In addition, Gilead was asked to submit proposed labeling based on these findings.

In addition, there was general agreement regarding the phenotypic analyses conducted by the Division and Gilead. The Divisions analyses only include those patients in studies 902 and 907 whose baseline phenotype was derived with the  assay (n=100), whereas Gilead pooled all patients (n=109). The Division requested further documentation regarding the appropriateness of pooling results from two different phenotype assays.

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

IND: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: April 25, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: FRACTURE DATA FORMAT FOR NDA SUBMISSION AND SAFETY UPDATE

Please refer to your ~~XXXXXXXXXX~~ for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection

Please refer to the table listed below for the format for reporting bone fracture information in both your upcoming NDA submission and the August safety update:

Bone Marrow Adverse Events

PT ID	SEX	AGE	RACE	DATE OF EVENT	FX SITE	HISTORY*	TX GROUP	DAYS TO EVENT	RISK FACTORS

*HISTORY: Please include all relevant lab data and investigator narrative/summary and assessment; Data should include:
(1) menopausal/gonadal status;

- (2) use of relevant concomitant medications (e.g., glucocorticoids);
- (3) thyroid status;
- (4) serum calcium, phosphorus, vitamin D (if available), creatinine; urinary calcium, and phosphorus (if available);
- (5) bone mineral density; and
- (6) radiological confirmation of fracture.

We are providing the above information via telephone facsimile for your convenience.

THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.

Please feel free to contact me if you have any questions regarding the contents of this transmission.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: May 9, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader and Acting Division Director

Subject: **FORMAT FOR SUBMISSION OF RESISTANCE DATA**

Please refer to your [redacted] for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000.

The following template should be used when you submit your resistance data:

FORMAT FOR SUBMISSION OF RESISTANCE DATA

For each study please construct datasets as SAS transport files containing the following information. Please include one record (row) per patient per isolate (e.g., baseline, failure, etc) For genotype baseline and follow up isolates will be on separate records per patient. However please retain phenotypic data, baseline and follow up data, for every record.

Suggested Column Headings

Patient Data:

1. Patient identification number
2. Previous therapeutic agents from the same class as the candidate drug

3. Treatment group

Endpoint Data:

4. HIV RNA (copies/mL) at baseline
5. HIV RNA (copies/mL) at week 24 (or other predefined timepoint)
6. HIV RNA (copies/mL) at week 48 (or other predefined timepoint)
7. HIV RNA (copies/mL) at time of loss of virologic response
8. Endpoint assessment (e.g., DAVG, mean change from baseline, etc) **NOTE: ONLY INCLUDE IF ENDPOINT WAS NOT PROPORTION < 400 OR < 50 COPIES/ML**

Genotypic Data:

9. Genotype information for all the RT/PI or relevant coding region that was sequenced, one amino acid per column. Changes from WT standard sequence indicated (i.e., blanks indicate no change). The information should be given for both candidate drug and all other antiretroviral agents in the regimen.

Example: Note this example highlight how genotype information should be displayed and does not include all column headings as suggested above.

Patient #	Isolate	82-V	83-N	84-I	85-I	86-G	87-R	88-N	89-L	90-L
001	BASE			V				S		M/L
002	BASE	A/T		V				D		M
003	BASE	T		V						
004	BASE			V						M

Phenotypic Data:

10. Baseline EC50 for candidate drug
11. Baseline EC50 for other antiretroviral agents in the regimen
12. Baseline EC50 compared to reference strain for candidate drug
13. EC50 at time of endpoint assessment or failure for candidate drug
14. EC50 at time of endpoint assessment or failure compared to WT or reference strain for candidate drug.
15. Change in EC50 from baseline at time of endpoint assessment or failure for candidate drug
16. Change in EC50 from baseline at time of endpoint assessment or failure for other antiretroviral agents in the regimen
17. Change in EC50 relative to WT for all other antiretroviral agents in the regimen (i.e. other than candidate drug)
18. Change in EC50 relative to WT or reference strain for each of the approved/investigational agent(s) in the same class

We are providing the above information via telephone facsimile for your convenience.

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

IND: [redacted] NDA 21-356

Drug: Tenofovir DF for the treatment of HIV infection

Date: May 14, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader, Acting Deputy Director
Linda L. Lewis, MD, Medical Officer

Subject: REQUEST FOR SUBMISSION OF PEDIATRIC PROTOCOL

Please refer to your [redacted] for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to SN-202 requesting approval of a protocol exception for study GS-00-955 entitled "*Tenofovir Expanded Access Protocol (EAP)*." Reference is also made to the pre-NDA meeting of April 20, 2001 between Gilead and the Division, and to the pre-meeting background materials SN-186 dated March 21, 2001.

To date studies in pediatric patients have not been initiated due to the concerns of bone toxicity and limited data in adults. During the meeting, you proposed to conduct a pharmacokinetic, safety, and activity trial in pediatric patients with limited therapeutic options. You proposed that the study be conducted by the National Cancer Institute at a single center. At the meeting, we indicated that we would defer further discussions to a later date. After additional consideration, we feel it is reasonable to proceed with a study conducted at a single site in children with limited therapeutic options. The protocol should also include a detailed bone-monitoring plan. Please send your plans to us as soon as possible. We are committed to a rapid review of this protocol.

We are providing the above information via telephone facsimile for your convenience.

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

IND: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: May 17, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: LABELING FORMAT FOR NDA SUBMISSION

Please refer to your Investigational New Drug (IND) application for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your proposed new drug application (NDA) 21-356 for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated April 30, 2001.

Please consider the following labeling changes:

1. Please provide your opinion, including supporting data and rationale regarding the inclusion of the following nucleoside analogue class box warning:

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING DRUG X AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

2. Please include a section titled "ANIMAL TOXICOLOGY" in your proposed package insert. This section should adequately describe the pre-clinical findings of bone toxicity. Please refer to the *Rescriptor* label as an example where this section is included.

3. Please include statements about the potential for bone abnormalities, including fractures. Also, please propose which section of the label this information should be included.
4. Please move the text containing resistance information from the "**Description of Clinical Trials**" section to the "**Microbiology**" section. For an example, please refer to the *Kaletra* label.
5. Please prepare a patient package insert. Again, please refer to the *Kaletra* patient package insert as an example.

We are providing the above information via telephone facsimile for your convenience.
THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.
Please feel free to contact me if you have any questions regarding the contents of this transmission.

**APPEARS THIS WAY
ON ORIGINAL**

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: May 25, 2001

To: Rebecca Coleman, PharmD, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Sean J. Belouin, R.Ph., Regulatory Project Manager/HFD-530

Through: Greg Soon, Ph.D., Statistical Team Leader/HFD-530
Rafia Bhore, Ph.D., Statistician/HFD-530

Subject: NDA 21-356/SN-000: Statistical comments regarding Protocols 902 and 907

The following statistical comments are being conveyed on behalf of Greg Soon, Ph.D., and Rafia Bhore, Ph.D:

1. Please provide the following items related to Protocols 902 and 907 submitted under NDA 21-356 (tenofovir DF).
 - Programs for transforming raw data into intermediate analysis datasets. (If intermediate analysis datasets have not been provided with the NDA submission, then please provide them as SAS transport files.)
 - Programs, algorithms, and macros (if any) using intermediate analysis datasets to get efficacy results.
 - Programs for obtaining results on safety parameters.
2. Please include comments in programs and algorithms to make them readable and understandable.
3. Please include documentation describing the list of programs, algorithms, and macros (if any).
4. Please provide the above information through electronic files on CD-ROM. All programs and other files must be compatible with Windows 95 and PC SAS version 6.12.

NDA 21-356/SN-000
May 25, 2001

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Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: May 30, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jooran, Kim, Pharm D, Pharmacokinetics Reviewer

Concur: Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader
Linda L. Lewis, MD, Medical Officer Team Leader (Acting)

Subject: REQUEST FOR CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS DATA

Please refer to your [redacted] for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000.

Please submit the following information as soon as possible:

1. Complete, individual pharmacokinetic data of all measured parameters in usable, electronic format (as SAS transport files) for the following clinical studies: GS-97-701, GS-97-901, GS-99-907, GS-00-909 and GS-00-914. For Study GS-96-701 and Study GS 97-901, please include safety (e.g., adverse events) and efficacy (e.g., HIV RNA measurements and CD4 counts) data with the pharmacokinetic data for each subject. All datasets should include patient identifiers, demographic information and concomitant medications.
2. The dissolution specification for tenofovir DF tablets, 300 mg may not be acceptable at a Q value set at 45 minutes. Summary dissolution data (previously submitted February 15, 2001) indicate a specification of Q=[redacted] at 30 minutes is appropriate. Please submit individual tablet data for at least 12 tablets per batch. Include data from the batch used in the pivotal bioequivalence study.

3. A full report of your permeability data for tenofovir in Caco-2 cell monolayers.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: June 19, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jooran, Kim, Pharm D, Pharmacokinetics Reviewer

Concur: Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: CLARRIFICATION OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS DATA FORMAT

Please refer to your for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000. Reference is made to NDA 21-356 SN-020 requesting clarification of pharmacokinetic (PK) database descriptions dated June 5, 2001.

Please submit PK raw data for review. All of the clinical raw data should also be submitted for each patient who has any PK data. Reference to the PK software package may be made. PK formulae do not need to be provided.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir (TNV) DF for the treatment of HIV infection

Date: July 2, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader and Acting Division Director

Subject: AGENDA FOR JULY 6, 2001 TELECONFERENCE (TCON)

Please refer to your [redacted] for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000.

In order for you to prepare for the TCON scheduled for Friday, we want to convey to you the data analyses we have done.

GENOTYPE ANALYSES:

1. For the zidovudine (ZDV) mutations, 41L, 67N, 210W, 215Y/F, 219 Q/E/N mean DAVG24 responses were calculated for patients with any one of these mutations present or absent at baseline for both treatment groups.
2. DAVG24 was calculated for the common ZDV mutational patterns found at baseline: (67+70+ 219); (41+215; 41+210+215); (67+70+215+219); and (41+67+210+215.)
3. Overall conclusion: Patients with 41L, or 210W or 215 Y/F at baseline had a lower DAVG24 compared to patients who did not have these mutations present at baseline. We want to discuss possible labeling implications for these analyses.

4. The above analyses were also done with the presence of the 184 mutation at baseline.
5. DAVG24 was also calculated for both groups by number of ZDV mutations present at baseline

PHENOTYPE ANALYSES:

6. DAVG24 was calculated for baseline phenotype fold change from wild type for ZDV, TNF, abacavir, stavudine, and didanosine. The mean fold change at baseline was used for the cutoffs. For example, the mean fold change at baseline for abacavir was 4.

For the TNV Group:	Fold Change abacavir	DAVG24
	<= 4	-0.66
	> 4	-0.28

We want to discuss the possible labeling implications for these analyses.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir Disoproxil Fumerate

Date: July 3, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Rao V. Kambhampati, PhD, Chemist

Concur: Stephen P. Miller, PhD, Chemistry Team Leader
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC): REVIEW COMMENTS AND RECOMMENDATIONS

Please refer to your [redacted] for tenofovir disoproxil fumerate (TNV DF; PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2001.

On Monday, July 2, 2001, a teleconference (TCON) was held to discuss CMC issues associated with TNV DF. The following individuals participated in the discussion:

- Gilead Sciences -
Robert Simon, MD, Vice President, Global Regulatory Affairs
- DAVDP -
Rao V. Kambhampati, PhD, Chemist
Stephen P. Miller, PhD, Chemistry Team Leader,
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager

As promised, we are sending you a list of general CMC comments and recommendations in this facsimile. Comments and recommendations regarding Gilead's proposed limits in the specifications for the drug substance and drug product will be provided as soon as possible.

Please address the following CMC review comments and recommendations:

DRUG SUBSTANCE:

[Redacted]

2. Please provide the manufacturing differences (relative to the final commercial process) for the fifteen batches that were used for the stability studies. For example, differences in [Redacted] Please summarize these data in a table and identify the primary and supportive stability batches.
3. Please provide a commitment to place two additional production batches for each site for the stability study.
4. In the specifications, please include a limit for the total [Redacted]

[Redacted]

7. Please provide updated stability data for all the batches when available.

DRUG PRODUCT:

8. In the batch analyses at release for tenofovir disoproxil fumarate tablets, please include a table for all individual impurities contents and unspecified impurities contents.
9. Please provide 3- and 6-month accelerated stability study results of the Lots J005B1, J006B1, J007B1, and J008B1 when available.
10. Please provide 12-month long-term stability study results of the Lots J001B1 and J002B1 when available.
11. Please provide the available release and stability study results of tenofovir DF tablets that were manufactured at [Redacted] using the drug substance manufactured at [Redacted]

12. You have indicated that the 18-month long-term stability testing for Lots J001B1 and J002B2 is scheduled in November 2001 (Volume 6, pages 93.) The PDUFA goal date for the NDA is November 1, 2001. Therefore, we believe that the 18-month long-term stability data will not be available for these lots prior to the goal date of November 1, 2001.

13. In the Study Summary Section of the Stability Study Report #AC-STAB-029.00 (Vol.6, pages 96-97), you have stated that 12-month long term data were presented for five primary stability batches, however, the data were actually submitted for two batches only (J904D and J905 D1). You have also stated that the accelerated stability data were presented for nine batches, however, the data were actually provided for five batches only. Please clarify these discrepancies

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**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: July 24, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader and Acting Division Director

Subject: SUBMISSION OF BONE FRACTURE ANALYSES PRIOR TO MEETINGS

Please refer to your [redacted] for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000.

Please conduct the following analyses and submit the results prior to our internal review team meeting on August 6, 2001, if possible. Also, please submit the datasets used to conduct these analyses. Please provide results for each study individually (902 and 907) and for both studies combined. All analyses should include all fractures regardless of dose and should include the ITT population. For example, if a patient develops a fracture in study 910 but was originally randomized to study 902, then the fracture should be included in the 902 analyses. Please calculate the following:

1. Six-month interval bone fracture rates (similar to the analysis submitted in SN-040 but using the criteria outlined above). Please include time interval, number of patients, number of fractures, total exposure (person-years), and fracture rate (95% CI)
2. One-year interval bone fracture rates. Please include time interval, number of patients, number of fractures, total exposure (person-years), and fracture rate (95% CI)

3. Individual, patient-level data containing time to fracture, treatment group, date randomized, and data cut-off date.
4. Kaplan-Meier curves for time to fracture for placebo and tenofovir DF groups

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356

Drug: Tenofovir DF for the treatment of HIV infection

Date: July 26, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jooran Kim, Pharm D, Pharmacokinetics Reviewer

Concur: Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR INFORMATION ABOUT RENAL INSUFFICIENCY PROTOCOL

Please refer to your **[REDACTED]** for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 dated April 30, 2001.

We have the following request for further information:

Since tenofovir is primarily eliminated through the kidneys, results from your renal impairment study should be provided as soon as possible in order to provide adequate dosing recommendations for patients with renal insufficiency. Please indicate when you plan to conduct this study and when the results will be available. Also, please provide the study protocol as soon as possible.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: July 26, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer
Rafia Bhore, PhD, Mathematical Statistician

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader
Greg Soon, PhD, Biometrics Team Leader

Subject: REQUEST FOR SUBMISSION OF OUTCOMES OF RANDOMIZED TREATMENT THROUGH WEEK 24 FOR STUDIES 902 AND 907 IN TABULAR FORM

Please refer to your  for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000.

Please complete the following table for Studies 902 and 907. This information will be used in the Description of Clinical Trials Section for the Package Insert. Also, please send us the program and names of datasets used to create these tables.

Outcomes of Randomized Treatment Through Week 24 (Study XXX)

Outcome	Placebo (N=XX)	Tenofovir 300 mg (N=XX)
HIV RNA <400 copies/mL HIV RNA ≥400 copies/mL Discontinued due to adverse reactions Discontinued due to other reasons [†] Missing HIV RNA Level	XX%	XX%

[†]Includes discontinuations due to consent withdrawn, lost to follow up, non-compliance, protocol violations, pregnancy, and other reasons.

Outcomes of Randomized Treatment Through Week 24 (Study XXX)

Outcome	Placebo (N=XX)	Tenofovir 300 mg (N=XX)
HIV RNA <50 copies/mL HIV RNA ≥50 copies/mL Discontinued due to adverse reactions Discontinued due to other reasons [†] Missing HIV RNA Level	XX%	XX%

[†]Includes discontinuations due to consent withdrawn, lost to follow up, non-compliance, protocol violations, pregnancy, and other reasons.

XX patients in the tenofovir arm and XX patients in the placebo arm experienced a new CDC Class C event

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir DF for the treatment of HIV infection

Date: August 6, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer

Concur: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader and Acting Division Director

Subject: REQUEST FOR INFORMATION FROM SPONSOR FOR DISCUSSION AT MEETING SCHEDULED 08/10/2001

Please refer to your [redacted] for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2000.

Please address the following comments during your presentation to the Division at the meeting scheduled for August 6, 2001:

1. Please discuss what clinical chemistries are being collected in your long-term monitoring plan.
2. Study 902 states that vitamin D levels were to be collected. Was this information collected? If so please send us these data prior to Friday's meeting. Were vitamin D levels collected in study 907? Were any other biochemical markers collected in these studies? If so please provide these data.
3. Please provide a list of the specific serum and urine bone biochemical markers that you are evaluating in study 903.
4. Please provide additional information on how patient-years were calculated. Based

on the datasets provided, the statistical reviewers are not able to duplicate the values provided.

5. Please explain how you handled fractures that were not confirmed by radiograph. In studies 902 and 907, we found a total of 16 fractures in the tenofovir group, of which one was not confirmed by radiograph. Your analysis lists 15 fractures. However in the placebo group only 1 fracture was confirmed.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-356/SN-000

Drug: Tenofovir Disoproxil Fumarate

Date: August 17, 2001

To: Rebecca Coleman, Pharm D, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Rao V. Kambhampati, PhD, Chemist

Concur: Stephen P. Miller, PhD, Chemistry Team Leader

Subject: CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC): COMMENTS AND RECOMMENDATIONS RELATED TO BOTTLE AND CARTON LABELS

Please refer to your [redacted] for tenofovir disoproxil fumarate (Tenofovir DF; PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2001.

The VIREAD bottle, box, and package insert labeling should contain the following:

VIREAD
(tenofovir disoproxil fumarate)
Tablets
245 mg

OR

VIREAD Tablets
(tenofovir disoproxil fumarate tablets)
245 mg

Bottle and Carton Labels: Each tablet contains tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

Package Insert: Each tablet contains 300 mg of tenofovir disoproxil fumarate which is equivalent to 245 mg of tenofovir disoproxil.

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MEMORANDUM OF TELECON

DATE: June 4, 2001
APPLICATION NUMBER: NDA 21-356 Tenofovir DF

BETWEEN:

Name: Rebecca Coleman, Pharm D, Director, Regulatory Affairs
Phone: 650-522-5831
Representing: Gilead Sciences, Inc

AND

Name: Kimberly A. Struble, Pharm D, Regulatory Review Officer
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project
Manager
Division of Antiviral Drug Products HFD-530

SUBJECT: INTERPRETATION OF DATASETS FOR PROTOCOL 902

This teleconference (TCON) was held to discuss discrepancies between Gilead's study 902 renal insufficiency data and those of Dr. Struble. Dr. Struble included two patients with increased creatinine levels in her analysis. Gilead's analysis included data taken on protocol-specified dates and from the central laboratory. There may be cases where laboratories were collected during hospitalization and not by the central laboratory. Gilead has laboratory data from both the central laboratory and other laboratories. Gilead will review these data and identify patients with renal abnormalities. This evaluation will also be done for Study 907. Gilead will submit these data as soon as possible.

Marsha S. Holloman, BS Pharm, JD

MEMORANDUM OF TELECON

DATE: July 6, 2001

APPLICATION NUMBER: NDA 21-356/

BETWEEN:

Participants: Shan-Shan Chen, MPH, Associate Director, Biostatistics
Norbert Bischofberger, PhD, Senior Vice President, Research and Development
Rebecca Coleman, Pharm D, Director, Regulatory Affairs.
Michael Miller, PhD, Director, Virology
Michael O'Beirne, MS, Manager, Regulatory Affairs
Michael Wulfsohn, MD, PhD, Sr. Director, Biometrics and Data Management

Phone: 650-522-5486
Sponsor: Gilead Sciences, Inc.

AND

Participants: Kimberly A. Struble, Pharm D, Regulatory Review Officer/DAVDP
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader/DAVDP
Narayana Battula, PhD, Microbiologist/DAVDP
Sean J. Belouin, R.Ph, Regulatory Project Manager/DAVDP
Emily Wu, PharmD, Fellow

Phone: 301-827-2335
Division: Antiviral Drug Products, HFD-530

SUBJECT: DISCUSSION OF RESISTANCE DATA, CD₄ RESPONSES FOR STUDIES 902
AND 907, AND FDA REVIEW OF RENAL PARAMETERS FOR TENOFOVIR
(TNV) DF

BACKGROUND:

This teleconference was requested by the Division to discuss the following issues. Please refer to the facsimile dated July 2, 2001.

- Discussion of genotypic and phenotypic analyses conducted by the Division and potential labeling implications.
- CD₄ responses for studies 902 and 907
- FDA review of renal parameter data

DISCUSSION:

1. Gilead agreed to conduct the FDA proposed genotype and phenotype analyses as outlined in the July 2, 2001 facsimile. There was generally agreement that patients with the ZDV mutations 41L, 210W or 215Y/F at baseline had a lower DAVG24 compared to patients who did not have these mutations present at baseline. In addition, the number of ZDV mutations at baseline also affected virologic response.
2. It was agreed that the genotype and phenotype data from studies 902 and 907 would be pooled together and a qualitative assessment of the data would be included in the microbiology section of the label. A teleconference will be scheduled at a later date to discuss labeling.
3. For renal parameters, given the available data, DAVDP concluded that tenofovir caused no significant renal toxicity. The majority of the phosphate abnormalities observed were isolated events. DAVDP pointed out that another antiretroviral from the class of nucleotide analogues, adefovir, was associated with delayed nephrotoxicity. It will be important to assess long term changes in renal parameters over time. This assessment will most likely be part of the accelerated approval or phase IV commitment plans.
4. Regarding CD₄ cell counts in studies 902 and 907, DAVDP suggested that the sponsor provide a detailed assessment of the CD₄ results in the advisory committee backgrounder and in their presentation. Overall mean changes from baseline were small, however, patients with lower CD₄ cell counts at baseline had larger increases at week 24 compared to those patients with a higher baseline CD₄. Gilead pointed out that two other studies, one with abacavir and the other with T-20, showed similar and consistent results like that of tenofovir, thus arguing that tenofovir was no exception.
5. For bone toxicity, Gilead and DAVDP agreed to discuss at a later teleconference the long term risks associated with tenofovir and how that might impact labeling. Gilead agreed to send in analyses of risk fractures when completed.
6. Lastly, regarding laboratory abnormalities, Gilead agreed to revise the Laboratory Abnormality Table in the package insert to include CK > 4 times the upper limit of normal.

Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MEMORANDUM OF TELECON

DATE: August 2, 2001

APPLICATION NUMBER: NDA 21-356/S-047, VIREAD (tenofovir disoproxil fumarate)

BETWEEN:

Name: Rebecca Coleman, Pharm D, Director, Regulatory Affairs
Phone: 650-522-5831
Representing: Gilead Sciences, Inc

AND

Name: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager
Kimberly A. Struble, Pharm D, Regulatory Review Officer
Division of Antiviral Drug Products, HFD-530

SUBJECT: RFI from Gilead for recalculation of datasets in SN-047 dated August 2, 2001.

Dr. Struble requested that Gilead recalculate the datasets as follows:

1. For the table entitled "*Fracture Rate Calculation, Safety Update Database Cut from Studies 902 and 907 Combined,*" please calculate 0-6, >6-12, and >12 time intervals for both drug and placebo.
2. For the table entitled "*Fracture Rate Calculation, Safety Update Database Cut from Studies 902,*" please calculate 0-6, >6-12, and >12 time intervals for both drug and placebo.
3. In the Kaplan-Meier Analyses, please use a scale of 25% on the Y-axis (percentage of bone fractures).

When reminded that the internal review team meeting to discuss these data is scheduled for Friday, August 3, Dr. Coleman said she would try to email the changes to us by tomorrow morning.

Marsha S. Holloman, BS Pharm, JD
Regulatory Health Project Manager

MEMORANDUM OF TELECON

DATE: August 14, 2001

APPLICATION NUMBER: NDA 21-356

BETWEEN:

Participants: Rebecca Coleman, Pharm D, Director, Regulatory Affairs
Jay O'Toole, MD, PhD, Vice President Clinical Research

Phone: 650-522-5486

Sponsor: Gilead Sciences, Inc.

AND

Participants: Kimberly A. Struble, Pharm D, Regulatory Review Officer
Jeffrey S. Murray, MD, MPH, Acting Deputy Director
Grace N. Carmouze, Regulatory Project Manager

Phone: 301-827-2335

Division: Antiviral Drug Products, HFD-530

SUBJECT: Gilead Sciences' Advisory Committee Presentation

BACKGROUND:

The applicant requested a teleconference with the Division to discuss their slide presentation for the DAVDP Advisory Committee meeting in October 2001. The applicant faxed a draft version of their presentation prior to the teleconference.

DISCUSSION:

The Division provided comments and recommendations to the applicant's proposed slide presentation. The Division stressed to the applicant that they should be as forthcoming with all tenofovir data.

Regarding the proposed questions to the committee, the Division stated that there were four topics being considered for discussion, indication, general clinical virology issues, preclinical and clinical bone abnormality assessment and the second confirmatory study. The Division is considering not having a "vote" question regarding approvability. Instead, a question regarding which patient population should tenofovir be recommended may be considered. The applicant queried the Division as to the purpose of having an advisory committee meeting if the Agency agrees with the safety and efficacy data and is considering a "no-vote" meeting. In response, the Division stated that the meeting would be a means to publicly comment on the following:

- Bone abnormalities: Assessment of the preclinical and clinical data; recommendations for additional preclinical and/or clinical studies to address the potential for bone abnormalities and comments on the applicant's long-term monitoring for this potential toxicity.

- Clinical Virology: The types of clinical virology analyses conducted and proposals for inclusion of resistance data into the package insert.
- The applicant's proposed second confirmatory study and suggestions for alternative study designs or patient populations that should be studied.
- Proposed Indication: Recommendations regarding which patient population should tenofovir be recommended.

The Division noted that, although individual bone fracture data will be included in their background package, a discussion of individual cases would not be part of the FDA presentation. If this is subject to change, the Division will let the applicant know.

As a follow up to the November 1999 resistance AC meeting, the Division stated they are interested in seeking public comment on the inclusion of resistance data in the label. The applicant inquired if the Division would solicit public comment. The Division stated that people are free to make comments during the open public hearing but would not ask individuals, other than AC members and guests, to make specific comments on this issue during the meeting.

The applicant asked when the Agency's backgrounder would be made public. The Division stated that they would contact the advisors and consultants office for specific details.

The Division reminded the applicant that the Agency cannot share its presentation in hard copy to applicants prior to the Advisory Committee. However, specific details can be discussed via telephone.

The applicant indicated that they are still working on providing the information that was requested during the August 10, 2001 meeting and in previous teleconferences/facsimiles.

Grace N. Carmouze
Regulatory Project Manager