DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-356/S-025

GILEAD SCIENCES, INC.
Attention: Nikki McMillan
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. McMillan:

Please refer to your supplemental new drug application dated October 11, 2007, received October 11, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viread® (tenofovir disoproxil fumarate) Tablets.

We acknowledge receipt of your submissions dated January 8, 2008, February 8, 2008, February 15, 2008, March 12, 2008, March 25, 2008, March 26, 2008, April 8, 2008, May 1, 2008, May 23, 2008, May 29, 2008, May 30, 2008, June 5, 2008, June 19, 2008, June 23, 2008, July 24, 2008, August 6, 2008 and August 8, 2008.

This supplemental new drug application provides for the use of Viread (tenofovir disoproxil fumarate) for treatment of Chronic Hepatitis B.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies in patients 12 to 18 years of age until JANUARY 2013 because this product is ready for approval for use in adults and the pediatric studies have not been completed.

We are deferring submission of your pediatric studies in patients 2 to <12 years of age until JANUARY 2014 because this product is ready for approval for use in adults and the pediatric studies have not been completed.

We are deferring submission of your pediatric studies in patients from birth to <2 years of age until JANUARY 2018 because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Due to concerns for the potential for bone toxicity in rapidly growing infants

and young children, we anticipate waiting for completion and review of studies in pediatric patients 2 to < 18 years age before determining whether it is appropriate to study tenofovir DF for HBV in the birth to <2 years age group. According to experts in pediatric HBV disease (pediatric hepatologists), treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this group may be waived in the future if this continues to be the consensus opinion at the time the safety data is available or if the risk/benefit assessment is not favorable based on safety data from older pediatric patients.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. Deferred pediatric studies under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 12 to < 18 years of age.

Protocol Submission:	COMPLETED
Study Start Date:	ONGOING
Final Report Submission:	JANUARY 2013 (72 week data)

2. Deferred pediatric studies under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages 2 to <12 years of age.

Protocol Submission:	OCTOBER 2009
Study Start Date:	DECEMBER 2009
Final Report Submission:	JANUARY 2014

3. Deferred pediatric study under PREA for the treatment of chronic hepatitis B virus infection in pediatric patients ages birth to <2 years of age.

   Review of available pediatric data in HBV; decision on risk/benefit and appropriateness of study: March 2014

Protocol Submission:	MAY 2014
Study Start Date:	SEPTEMBER 2014
Final Report Submission:	JANUARY 2018

Submit the protocols to your IND 71,576, with a cross-reference letter to this NDA 21-356. Submit all final reports to your NDA 21-356. Use the following designator to prominently label all submissions:

- **Required Pediatric Assessment(s)**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since Viread was approved in October 2001 for the treatment of HIV-1 infection, we have become aware of the serious risk for potential drug resistance creating the loss of alternative treatment options for hepatitis B and subsequent treatment failure or flare of hepatitis-B-related hepatic disease. These risks have been observed with other nucleoside analogs which have activity against hepatitis B virus. By studying analyses from virologic treatment failure patients, FDA can better determine appropriate use of Viread in order to inform patient selection, and decrease the likelihood of developing resistance and of hepatitis B flares. In addition, this information will also help with our understanding of mutations that may confer resistance to other hepatitis B options. This information was not relevant to Viread when marketing authorization was granted for the treatment of HIV-1 infection. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk, that is, the development of resistance to a drug in those organisms specific to the labeled indication, resulting in the increased serious risk of potential loss of alternative treatment options and subsequent treatment failure or flare of hepatic disease.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study:

4. Perform annual genotypic and phenotypic analyses of HBV DNA from subjects who experience virologic failure to long-term TDF therapy (serum HBV DNA levels ≥400 copies/mL) in ongoing clinical trials out to 240 weeks (Studies 0102 and 0103) and 168 weeks (Study 0106). Submit a virology study report and cumulative resistance dataset each year.

The timetable you submitted on August 8, 2008, states you will conduct this study according to the following schedule:

Protocol Submission:	COMPLETED
Study Start:	ONGOING
First Annual Virology Report:	SEPTEMBER 2009 (96 week data from 0102 and 0103; 48 week data from 0106)
Final Report Submission:	FEBRUARY 2012 (0102); JULY 2011 (0106)

Submit the protocols to your IND 71,576, with a cross-reference letter to this NDA 21-356. Submit all final reports to your NDA 21-356. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirement as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study and clinical trial commitments agreed to in your submission dated August 8, 2008:

5. Determine the susceptibility to tenofovir in cell culture of HBV harboring individually the following substitutions of conserved amino acid residues among HBV isolates: rtH35P, rtY111C, rtH156R, and rtI233T. Also, evaluate the [redacted] polymorphisms. For any substitutions showing [redacted] fold shifts in susceptibility to tenofovir, determine the shifts in susceptibility to adefovir, entecavir, and lamivudine.

Protocol Submission:	DECEMBER 2008
Study Start:	FEBRUARY 2009
Final Report Submission:	MARCH 2010

6. Evaluate the use of tenofovir (TFV) versus TDF in susceptibility assays using isolates representing the range of susceptibilities.

Protocol Submission:	JANUARY 2009
Study Start:	MARCH 2009
Final Report Submission:	JULY 2010

Submit clinical protocols to your IND 71,576. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA 21-356. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing**

Commitment Protocol", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

CONTENT OF LABELING
As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. **For administrative purposes, please designate this submission, "SPL for approved NDA 21-356/S-025."**

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert).

PROMOTIONAL MATERIALS
You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS
If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS
We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Elizabeth Thompson, MS, Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure (clean copy of approved label)

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

/s/

Debra Birnkrant
8/11/2008 04:46:30 PM
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