DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 21-356
IND 71,576

GILEAD SCIENCES, INC.
Attention: Nikki McMillan
Senior Manager, Regulatory Affairs
4 University Place
4611 University Drive, Building 4
Durham, NC 27707

Dear Ms. McMillan:

To obtain needed pediatric information on Viread® (tenofovir disoproxil fumarate), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

BACKGROUND:

The requested studies investigate the potential use of tenofovir disoproxil fumarate in the treatment of pediatric patients 2 to < 18 years of age with chronic hepatitis B virus (HBV) infection.

Although universal hepatitis B virus vaccination is recommended in the United States and much of the rest of the world, chronic HBV infection remains a significant global health problem resulting in chronic liver disease, cirrhosis, hepatocellular carcinoma and death. There is no national surveillance program for chronic hepatitis B in children in the US, and the prevalence of this infection in not known but generally thought to be very low. Most children with chronic hepatitis B in the United States have acquired the infection vertically or were adopted from countries where the infection is endemic, or are adolescents with high risk behaviors. However, among pediatric patients who acquire HBV infection in the perinatal period, up to 95% are expected to develop chronic HBV infection. In the US, of those with chronic HBV, an estimated 5-10% spontaneously clear hepatitis B early antigen (HBeAg) each year making evaluation of treatment modalities difficult. Upon HBeAg clearance, the infection usually becomes inactive, although a few will later reactivate. Because the spontaneous clearance rate is significant but somewhat variable as reported in the literature, there is no consensus regarding optimal timing of treatment in pediatric patients, and because serious complications of chronic HBV often require years to develop, a placebo-controlled study allows clearer conclusions regarding efficacy without putting patients at undue risk. In adults, efficacy of HBV treatment is based on improvement in liver histology. Because of concern regarding the risk of liver biopsies in pediatric patients, non-histologic endpoints are appropriate in this age group. To date the only approved oral products for the treatment of chronic HBV in pediatric patients include, Epivir-HBV (lamivudine), approved for use in

pediatric patients 2 to 17 years of age, and Hepsera (adefovir dipovoxil), approved for use in patients 12 to 18 years of age. In addition, Intron A (interferon alfa-2b), an injectable product, is approved for use in pediatric patients 1 to 17 years of age. Each of these treatments has significant limitations including rapid development of resistance (Epivir-HBV), renal toxicity that limits dosing (Hepsera), and poor tolerability and safety profile (Intron A). Therefore, safe treatment, providing long-lasting antiviral activity is still needed for this population.

- *Nonclinical study(ies)*:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1: Conduct a randomized, double-blinded study evaluating the safety, tolerability and antiviral activity of tenofovir disoproxil fumarate compared to placebo in pediatric patients 12 to < 18 years of age with chronic HBV.

Study 2: Conduct a randomized, blinded study evaluating the safety, tolerability and antiviral activity of tenofovir disoproxil fumarate compared to placebo in pediatric patients 2 to < 12 years of age with chronic HBV.

In both studies, subjects must have evidence of chronic hepatitis B disease as documented by at least 6 months of documented hepatitis B surface antigen (HBsAg) positivity, hepatitis B e antigen (HBeAg) positivity, or measurable HBV DNA in the blood, accompanied by evidence of liver inflammation documented by abnormal liver transaminases or liver biopsy. Patients may be either HBeAg positive or negative. The study should enroll both treatment-naïve and treatment-experienced pediatric patients and randomization in the trial should be stratified according to prior treatment status.

Efficacy in pediatric patients 2 to < 18 years of age will be extrapolated from the efficacy (based on histologic endpoint) documented in adequate and well-controlled studies in adults presuming the antiviral activity in pediatric patients as measured by decrease in HBV DNA and serum ALT levels is similar to these measures observed in adults receiving tenofovir disoproxil fumarate for the same duration of treatment.

In order to better define the safety profile of tenofovir disoproxil fumarate and identify the appropriate dose, studies in pediatric HIV patients 12 to $\leq$ 18 years of age must be completed through at least 24 weeks of dosing before proceeding in patients with chronic HBV 12 to $\leq$ 18 years of age Studies in pediatric HIV patients 2 to $\leq$ 12 years of age must be completed through at least 24 weeks of dosing before proceeding in patients with chronic HBV 2 to $\leq$12 years of age in order to better define the safety profile of tenofovir disoproxil fumarate and identify the appropriate dose.

- *Objective of each study:*

Study 1: The objective of this study is to evaluate the safety, tolerability and antiviral activity of tenofovir disoproxil fumarate in the treatment of chronic HBV infection in pediatric patients 12 to ≤ 18 years of age.

Study 2: The objective of this study is to evaluate the safety, tolerability and antiviral activity of tenofovir disoproxil fumarate in the treatment of chronic HBV infection in pediatric patients 2 to ≤ 12 years of age.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*:
    Study 1: 12 to ≤ 18 years of age

    Study 2: 2 to < 12 years of age

  - *Number of patients to be studied:*
    Study 1: at least 100 subjects, randomized 1:1 (at least 50 receiving tenofovir disoproxil fumarate for 72 weeks)

    Study 2: at least 100 subjects randomized 1:1 (at least 50 receiving tenofovir disoproxil fumarate for 72 weeks)

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Pharmacokinetic Endpoints:
  - ☐ Sparse sampling to assess PK in pediatric age groups and document similarity to HIV infected pediatric patients receiving tenofovir disoproxil fumarate and to assess adherence

  Efficacy Endpoints;
  - ☐ The primary efficacy endpoint will be the proportion of subjects with HBV DNA < 400 copies/mL after 72 weeks of blinded treatment and must be assessed by HBV DNA PCR
  - ☐ Important secondary endpoints must include change in ALT and normalization of ALT and must be assessed by measurements of serum ALT, HBV DNA < 169 copies/mL, the proportion of patients who achieve HBeAg loss and seroconversion as assessed by HBeAg measurements, and the proportion of patients who achieve

HBsAg loss and seroconversion as assessed by HBsAg measurements, all assessed at Week 72.

Safety Endpoints:

- ☐ Safety outcomes must include: reporting of clinical adverse events, tolerability, vital signs, laboratory parameters, and growth parameters.
- ☐ The following adverse events must be actively monitored: hepatic flares and events potentially related to renal, bone or hepatic toxicity. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- ☐ A Data Monitoring Committee (DMC) must be included because of the possibility of serious toxicity with tenofovir disoproxil fumarate and the study is being performed in children, a potentially fragile population See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known Drug Safety concerns and monitoring:*

1. Renal, bone, or hepatic toxicity arising during dosing. Conduct a detailed assessment of possible mechanisms of bone toxicity in pediatric patients including:
   - Measurement of renal excretion of calcium, phosphorous, and magnesium through calculation of the renal phosphate threshold (TmP/GFR).
   - Measurement of urine bicarbonate, urine n-telopeptide, serum bone-specific alkaline phosphatase, parathyroid hormone, osteocalcin, c-telopeptide, 25 hydroxyvitamin D, 1,25 (dihydroxyvitamin) D levels, albumin, calcium, phosphate, magnesium, and bicarbonate.
   - Correlation of renal parameters with measurements of bone mineral density (DEXA).
2. Possible hepatic "flares" during or following therapy
3. Development of resistance mutations in HBV leading to loss of efficacy of tenofovir disoproxil fumarate and/or other drugs or to a "flare" of disease
4. Occurrence of complications of progressive liver disease such as disturbances of growth and development, decompensated liver disease, liver transplantation, and hepatocellular carcinoma (ie., lack of clinical efficacy)

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form: oral powder and tablets (multiple sizes)*

- *route of administration: oral*
- *regimen: dose to be determined by development program*

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

Randomized, controlled clinical trials with a placebo control group should have sufficient power to detect clinically meaningful differences in efficacy between drug and placebo in patients completing 48 to 72 weeks of treatment. The number of enrolled pediatric patients should also provide an adequate sampling to assess safety of the drug as noted above.

The primary analysis for both studies will evaluate the difference in the proportion of patients achieving HBV DNA < 400 copies/mL at Week 72 between the tenofovir and placebo groups. The sample size of 100 randomized 1:1 provides at least 80% power to detect a difference of 30% between the groups based on a 2-sided Fisher exact test with significance level of 0.05, assuming a response rate of 21% in the placebo group.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that tenofovir disoproxil fumarate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) or interim study reports describing the 72-week blinded treatment period that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Carrie Ceresa, Pharm D., MPH, Regulatory Project Manager, at 301-796-4108.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

EDWARD M COX
10/19/2010