DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21752/S-030

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Dara Wambach, MA
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your Supplemental New Drug Application (sNDA) dated December 14, 2011, received December 15, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets.

We acknowledge receipt of your amendments dated:

July 13, 2012	June 4, 2012	March 29, 2012
July 11, 2012	May 25, 2012	March 21, 2012
July 10, 2012	May 21, 2012	March 17, 2012
July 6, 2012	May 8, 2012	March 15, 2012
July 3, 2012	May 3, 2012	March 8, 2012
July 2, 2012	May 1, 2012	March 7, 2012
June 29, 2012	April 27, 2012	March 1, 2012
June 25, 2012	April 24, 2012	February 24, 2012
June 20, 2012	April 20, 2012	February 22, 2012
June 18, 2012	April 18, 2012	February 10, 2012
June 13, 2012	April 11, 2012	February 3, 2012
June 8, 2012	April 10, 2012	January 20, 2012
June 5, 2012	April 5, 2012	January 11, 2012

This "Prior Approval" supplemental new drug application proposes a new indication for the use of Truvada® in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 21752/S-030**." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Katherine Schumann
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6237
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Katherine Schumann
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6237
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

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 waiving the pediatric study requirement for this application for pediatric patients from birth to less than 16 years of age because necessary studies are impossible or highly impracticable. Based on the incidence, prevalence rate, and route of transmission of HIV, clinical trials of PrEP for prevention of HIV-1 infection would be highly impracticable in a general pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) authorizes 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 statute.

Since Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets was approved on August 2, 2004, we have become aware of the development of resistance-associated substitutions in HIV-1 viral isolates obtained from individuals with unrecognized acute HIV-1 infection who initiated Truvada® for pre-exposure prophylaxis of sexually acquired HIV-1 infection. The development of resistance-associated substitutions was observed in viral isolates obtained from individuals with unrecognized HIV-1 infection who enrolled in the iPrEx and Partners PrEP trials submitted in support of this sNDA application. We are also aware of the known serious risks of renal and skeletal abnormalities in patients treated with Truvada® for known HIV-1 infection, which must be evaluated in the context of the new population treated in the clinical trials submitted in support of this sNDA application. Finally, we have determined it is necessary to evaluate the potential for an unexpected serious risk of adverse maternal-fetal outcomes in uninfected women who become pregnant while taking Truvada® for a PrEP

indication, including risk for HIV seroconversions in mother and infants if Truvada® is discontinued because of pregnancy. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 the signal of a serious risk of development of drug-resistant HIV-1 variants in undiagnosed HIV-1-infected individuals who initiate or continue to take Truvada® for a PrEP indication after acquiring HIV-1 infection, the known serious risks of renal and skeletal abnormalities, or identify the unexpected serious risk of adverse maternal-fetal outcomes in women who become pregnant while taking Truvada® for a PrEP indication.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1906-1 Through collaboration with the Antiretroviral Pregnancy Registry, conduct a prospective observational study in order to collect and analyze data on maternal and fetal outcomes in 200 women who become pregnant while taking Truvada® for a pre-exposure prophylaxis (PrEP) indication and choose to continue Truvada® during their pregnancies and in 200 women who become pregnant while taking Truvada® for PrEP and choose to discontinue it. Collect and analyze data from at least a similarly sized comparator group of pregnant HIV-infected women taking antivirals other than emtricitabine/tenofovir disoproxil fumarate. Data collected on pregnancy outcomes should include but not be limited to: timing of initiation and duration of Truvada® or other antiretrovirals, HIV seroconversions in mothers and infants, spontaneous and elective abortions, spontaneous and scheduled pre-term deliveries, stillbirths, infant weight (normal or low) and infant outcomes, including the presence or absence of congenital malformations.

The timetable you submitted on July 6, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2012
Interim Report Submissions:	09/2013
	09/2014
	09/2015
	09/2016
Study Completion:	09/2016
Final Report Submission:	03/2017

Additionally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signal of a serious risk of development of drug-resistant HIV-1 variants in undiagnosed HIV-1-infected individuals who initiate or continue

to take Truvada® for a PrEP indication after acquiring HIV-1 infection, and the known serious risks of renal and skeletal abnormalities.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1906-2 Collect and analyze data from individuals who take Truvada® for pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who seroconvert during follow-up. The following data should be collected and the following analyses conducted on data collected from a minimum of 150 seroconverters over a time period not to exceed 3 years:

a. Data regarding the presence or absence of signs and symptoms of acute HIV infection at the study visit or since the last study visit when seroconversion is identified.
b. Frequency of screening and screening method(s) used for evaluation of the seroconverter, and in general, at that enrollment site.
c. Analyses of baseline samples from early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.
d. Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultrasensitive testing (such as ultra-deep sequencing of proviral DNA or allele-specific PCR) if no resistance is identified by population sequencing.

This data may be collected from individuals participating in demonstration projects (trials).

The timetable you submitted on June 28, 2012 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2012
Interim Report Submissions:	09/2013
	09/2014
	09/2015
Study Completion:	03/2016
Final Report Submission:	09/2016

1906-3 Conduct an analysis of data from ongoing and planned demonstration projects (trials) including at least 7000 uninfected individuals taking Truvada® for a pre-exposure prophylaxis (PrEP) indication with the objective of examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal adverse events. Levels of adherence should measure a gradient of adherence levels rather than the simple dichotomy of ‘adherent’ versus ‘non-adherent’ using any available data on drug levels as the measure of adherence. Seroconversion will be assessed every three months, and, upon each seroconversion, resistance testing should be performed. Assessment for renal and skeletal adverse events will be performed every three

months, including evaluation of available laboratory data. Analyses will be performed by geographic region, including the United States.

The timetable you submitted on July 11, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2012
Study Completion;	04/2016
Final Report Submission:	12/2016

Submit the protocols to your IND 108,930, with a cross-reference letter to this NDA. Submit all interim and final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We have received your letter dated July 11, 2012, stating your commitment to conduct the following postmarketing studies:

1906-4 Provide nationally representative drug utilization data to FDA of sufficient detail that use of Truvada® for a pre-exposure prophylaxis (PrEP) indication and individuals using Truvada® for a PrEP indication can both be characterized. These data should be submitted to FDA every 6 months for three years, for the combination product emtricitabine/tenofovir disoproxil fumarate, and for the single-ingredient products containing emtricitabine or tenofovir disoproxil fumarate, starting at one year following approval of the PrEP indication. The following analyses should be conducted with the data collected:

1) Total number of prescriptions dispensed across all settings of care
    a. Total number of prescriptions dispensed, stratified by indication, setting of care, and prescriber specialty
    b. Directions for use (signa) of prescriptions dispensed
2) Total number of unique patients receiving dispensed prescriptions across all settings of care
    a. Total number of unique patients receiving dispensed prescriptions, stratified by both indication and setting of care
        i. Unique incident users every quarter-year
        ii. Unique prevalent users every quarter-year
    b. Patient demographics of users of the product
    c. Clinical characteristics of users of the product
3) Duration of therapy, including definitions of gaps in drug therapy
    a. Total and stratified by indication
    b. Examination of possible 'intermittent' use
    c. Number of patients switching from PrEP to an HIV treatment regimen
    d. Dose adjustments
4) Comparison of drug utilization data collected to data collected from demonstration projects (trials) performed in the United States in terms of patient demographics, patient clinical characteristics, prescriber specialties, settings of care, and geographic region (when available).

The timetable you submitted on July 11, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2013
Interim Report Submissions:	07/2013
	01/2014
	07/2014
	01/2015
	07/2015
	01/2016
Final Report Submission:	07/2016

1906-5 In the context of a U.S. Centers for Disease Control and Prevention (CDC) demonstration project (trial) for once-daily Truvada® for a pre-exposure prophylaxis (PrEP) indication, validate an adherence questionnaire over the period of the demonstration project (trial) using an objective quantitative measure such as drug levels. In addition, the demonstration project (trial) will utilize subject demographics

and responses from a survey on knowledge, attitudes, and behaviors (sexual and non-sexual behaviors related to increased risk of HIV infection) in order to identify baseline characteristics associated with decreasing adherence, as measured via the adherence questionnaire and confirmed objectively by blood drug levels. The demonstration project (trial) will accrue 1200 individuals with an expected follow up of 12 months and use a national demographically representative sample that reflects the same target population described in 1906-4 above.

The timetable you submitted on July 11, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	07/2015
Final Report Submission:	02/2016

Submit clinical protocols to your IND 108,930 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all interim and final reports to this NDA. 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/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure the benefits of the drug outweigh its risks. Since Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets was approved on August 2, 2004, we have become aware of the new safety information described above.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Truvada® for a PrEP indication to ensure the benefits of the drug outweigh the risks of HIV-1 acquisition and development of resistance if Truvada® is initiated or continued in the setting of unrecognized HIV-1 infection.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR part 208. Pursuant to 21 CFR part 208, FDA has determined that Truvada® poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Truvada®. FDA has determined that Truvada® is a product for which patient labeling could help prevent serious adverse effects, that the Medication Guide is important to health, and that patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Truvada®.

Pursuant to 505-1(f)(1), we have also determined that Truvada® for a PrEP indication can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of HIV-1 acquisition and development of resistance if Truvada® for a PrEP indication is initiated or continued in the setting of unrecognized HIV-1 infection. The elements to assure safe use will inform and educate prescribers, other healthcare professionals and individuals at high risk for acquiring HIV-1 infection about:

- the importance of strict adherence to the recommended dosing regimen
- the importance of regulator monitoring of HIV-1 serostatus to avoid continuing to take Truvada® for a PrEP indication if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants; and
- the fact that Truvada® for a PrEP indication must be considered as only one part of a comprehensive prevention strategy in order to reduce the risk of HIV-1 infection and that other preventive measures should also be used.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, appended to this letter, is approved.

The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of uninfected individuals' understanding of the serious risks of Truvada®
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
3. Number of prescribers who completed the training and educational program via the Gilead website or through mailings
4. Demographics of prescribers and uninfected individuals taking Truvada® for the PrEP indication

5. Prescribers, by specialty type, who prescribe Truvada® for a PrEP indication, to the extent possible
6. Estimates of the total number of Truvada® prescriptions for a PrEP indication
7. Drug resistance in negative HIV-1 individuals who seroconvert to positive HIV-1 during use of Truvada® as monotherapy, to the extent possible
8. Compliance with regular HIV-1 testing (at least every 3 months) in individuals using Truvada® for a PrEP indication, to the extent possible
9. Comprehension testing of the REMS training and educational materials, including the Medication Guide.
10. Information received from adverse event reporting from spontaneous sources, published literature, regulatory agencies, clinical studies and trials (clinical serious adverse events/SAEs) and solicited sources for entry into the Gilead drug safety database.
11. Gilead will complete the following:
    a. Conduct a web-based phone and paper-based option, self-administered Knowledge, Attitude and Behavior (KAB) survey for prescribers and uninfected individuals taking (or who have recently taken) Truvada® for a PrEP indication. Surveys will assess prescriber and uninfected individuals understanding of the risks associated with use of Truvada® for a PrEP indication, their understanding of the importance of compliance as well as engaging in safer sex practices in order to assess the effectiveness of the REMS outreach and education.
    b. Develop and administer these surveys anonymously on a periodic basis to a random sample of uninfected individuals at high risk for acquiring HIV-1 infection currently taking (or who have taken) Truvada® for a PrEP indication and of prescribers who have registered to take the survey.
12. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g) of FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the

submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 21752 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

> **NDA 21752 REMS ASSESSMENT**
>
> **NEW SUPPLEMENT FOR NDA 21752**
> **PROPOSED REMS MODIFICATION**
> **REMS ASSESSMENT**
>
> **NEW SUPPLEMENT (NEW INDICATION FOR USE)**
> **FOR NDA 21752**
> **REMS ASSESSMENT**
> **PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

> Food and Drug Administration
> Center for Drug Evaluation and Research
> Office of Prescription Drug Promotion (OPDP)
> 5901-B Ammendale Road
> Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of

promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

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

ENCLOSURES:
Content of Labeling
Container Label
REMS

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

/s/

DEBRA B BIRNKRANT
07/16/2012