

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021752Orig1s030**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21752

SUPPL # 30

HFD # 530

Trade Name Truvada

Generic Name emtricitabine/tenofovir disoproxil fumarate

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known July 16, 2012

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) SE-1 new indication

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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

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

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

NDA# 21752 Truvada (emtricitabine/tenofovir disoproxil fumarate)

NDA# 21356 Viread (tenofovir disoproxil fumarate)

NDA# 21500 Emtriva (emtricitabine)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 8.

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.

(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 8:

(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: CO-US-104-0288, titled "Chemoprophylaxis for HIV Prevention in Men" (also known as the Pre-exposure Prophylaxis Initiative or "iPrEx" study)

Investigation #2: CO-US-104-0380, title "Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples" (also known as the "Partners PrEP" study)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

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

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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 #1: CO-US-104-0288, titled "Chemoprophylaxis for HIV Prevention in Men" (also known as the Pre-exposure Prophylaxis Initiative or "iPrEx" study)

Investigation #2: CO-US-104-0380, title "Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples" (also known as the "Partners PrEP" 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 # 71,859

YES

!  
!

! NO

! Explain:

The sponsor of this clinical investigation is the NIH Division of AIDS.

Investigation #2

IND # 75,365

YES

!  
!

! NO

! Explain:

The sponsor of this clinical investigation is the University of Washington International Clinical Research Center.

(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:

The applicant did not certify that they provided substantial support for the study. The applicant clearly attributes conduct/sponsorship of the study to another party (NIH Division of AIDS).

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

The applicant did not certify that they provided substantial support for the study. The applicant clearly attributes conduct/sponsorship of the study to another party (University of Washington).

(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

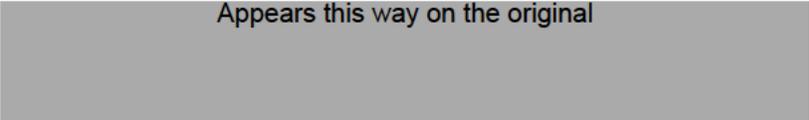
NO

If yes, explain:

=====  
Name of person completing form: Katherine Schumann, M.S.  
Title: Regulatory Project Manager, Division of Antiviral Products  
Date: June 20, 2012

Name of Office/Division Director signing form: Jeffrey S. Murray, M.D., M.P.H.  
Title: Deputy Director, Division of Antiviral Products

Appears this way on the original



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHERINE SCHUMANN  
06/25/2012

JEFFREY S MURRAY  
06/26/2012

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 21752 BLA #	NDA Supplement # 030 BLA Supplement #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: Truvada Established/Proper Name: emtricitabine/tenofovir disoproxil fumarate Dosage Form: tablet		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):
RPM: Katherine Schumann		Division: DAVP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>June 15, 2012, major amendment extension September 15, 2012</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input checked="" type="checkbox"/> None	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____	<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):  <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request  Comments:  BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies  REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input checked="" type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other FDA Voice Blog Post, Media Advisory, Fact Sheet

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul>	

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the

<p>Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	
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<b>CONTENTS OF ACTION PACKAGE</b>
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❖ Copy of this Action Package Checklist <sup>4</sup>	Included
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<b>Officer/Employee List</b>
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❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>
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❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval Letter, July 16, 2012
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<b>Labeling</b>
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❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	July 13, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	December 14, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	July 13, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	December 14, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	December 14, 2011
❖ Proprietary Name	DMEPA proprietary name memorandum dated June 22, 2012 (review evaluating AVDAC recommendation for a unique proprietary name for the PrEP indication)
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the ‘preferred’ name.</i></li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM July 16, 2012 <input type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DMPP/PLT (DRISK) June 22, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) Professional: June 25, 2012 Consumer: June 25, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	RPM Filing Review February 21, 2012  <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>April 18, 2012</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)</li> </ul>	Included
<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	Memoranda of Teleconferences: January 6, 2012 May 17, 2012 June 14, 2012
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg June 10, 2011
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg December 8, 2010
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	Type C meeting, October 28, 2009 Type C meeting, March 9, 2011
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	May 10, 2012
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	Not yet available

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 16, 2012
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 16, 2012
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 1906-1, July 16, 2012 1906-2, July 16, 2012 1906-3, July 16, 2012 1906-4, July 14, 2012 1906-5, July 14, 2012
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	July 13, 2012
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Included in Section 3.3 of clinical review dated July 13, 2012
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Post-market safety review, DPV, March 26, 2012 Drug utilization review, DEPI II, April 6, 2012 Epidemiology review, DEPI II, July 17, 2012 Maternal Health review, July 16, 2012
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	REMS Document: July 11, 2012 REMS Supporting Document: July 11, 2012 REMS Materials: July 11, 2012 and July 13, 2012 REMS Memo: July 13, 2012  DRISK Reviews: April 13, 2012 May 30, 2012 June 25, 2012 July 13, 2012
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	May 30, 2012

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None June 1, 2012
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 22, 2012
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 29, 2012 July 16, 2012 (Addendum)
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 10, 2012 July 16, 2012 (Amendment)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None May 21, 2012
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input checked="" type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	May 3, 2012
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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KATHERINE SCHUMANN  
07/17/2012

**From:** Schumann, Katherine  
**To:** ["Dara Wambach"](#)  
**Cc:** [Regulatory Archives](#)  
**Subject:** RE: NDA 21752 S-030 TRUVADA labeling  
**Date:** Friday, July 13, 2012 3:25:00 PM  
**Attachments:** [2012\\_07\\_13\\_labeling-text-clean.doc](#)

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Thanks, Dara.

I'm attaching a copy of the final labeling for your information. As we discussed, the revision date at the end of the PI was removed, as a revision date is already provided below the Highlights.

The revision date at the end of the Med Guide remains.

Thanks,

Katie

---

**From:** Dara Wambach [mailto:[Dara.Wambach@gilead.com](mailto:Dara.Wambach@gilead.com)]  
**Sent:** Friday, July 13, 2012 1:53 PM  
**To:** Dara Wambach; Schumann, Katherine  
**Cc:** Regulatory Archives; Paul Tomkins; Karin A Thacker  
**Subject:** RE: NDA 21752 S-030 TRUVADA labeling

Dear Katie,

In follow-up, please find attached a word document illustrating Gilead's acceptance of the final changes related to NDA 21-752/S-030.

Kind regards,  
Dara

---

**From:** Dara Wambach  
**Sent:** Friday, July 13, 2012 10:29 AM  
**To:** 'Schumann, Katherine'  
**Cc:** Regulatory Archives; Paul Tomkins; Karin A Thacker  
**Subject:** RE: NDA 21752 S-030 TRUVADA labeling

Dear Katie,

I have confirmed with my team and we agree to these changes as part of the final agreed-upon labeling for Truvada. We will plan to send a revised Word version of the PI via email later this afternoon.

Kind regards,  
Dara

---

**From:** Schumann, Katherine [mailto:[Katherine.Schumann@fda.hhs.gov](mailto:Katherine.Schumann@fda.hhs.gov)]  
**Sent:** Friday, July 13, 2012 9:38 AM  
**To:** Dara Wambach  
**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-030 TRUVADA labeling

Dear Dara,

As we discussed over the phone, I am attaching the labeling with several administrative/regulatory revisions in track changes. Please send me an email response indicating that Gilead agrees to these changes, so they can be made to the final approved labeling that will be appended to the action letter.

Please let me know if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: [Katherine.Schumann@fda.hhs.gov](mailto:Katherine.Schumann@fda.hhs.gov)

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/s/

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KATHERINE SCHUMANN  
07/15/2012

**From:** [Dara Wambach](#)  
**To:** [Dara Wambach](#); [Schumann, Katherine](#)  
**Cc:** [Regulatory Archives](#); [Paul Tomkins](#); [Karin A Thacker](#)  
**Subject:** RE: NDA 21752 S-030 TRUVADA labeling  
**Date:** Friday, July 13, 2012 1:52:56 PM  
**Attachments:** [2012-07-13 draft-labeling-clean.doc](#)

---

Dear Katie,

In follow-up, please find attached a word document illustrating Gilead's acceptance of the final changes related to NDA 21-752/S-030.

Kind regards,  
Dara

---

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Kind regards,  
Dara

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**Sent:** Friday, July 13, 2012 9:38 AM  
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**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-030 TRUVADA labeling

Dear Dara,

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Please let me know if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager

FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: [Katherine.Schumann@fda.hhs.gov](mailto:Katherine.Schumann@fda.hhs.gov)

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KATHERINE SCHUMANN  
07/13/2012

**From:** [Schumann, Katherine](#)  
**To:** ["Dara Wambach"](#)  
**Cc:** [Regulatory Archives](#); [Paul Tomkins](#)  
**Subject:** RE: NDA 21-752-S-30 - Proposed Alternative Text to Section 5.9 in Truvada PI  
**Date:** Tuesday, July 10, 2012 5:16:00 PM

---

Dear Dara,

The Division has reviewed your proposed change to Section 5.9 of the TRUVADA labeling, as written below:

§ While using TRUVADA for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, (b) (4)  
 using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

While we understand your concern that this may prompt unnecessary interruptions in PrEP, we believe the risk that individuals who are acutely infected may develop resistance, particularly the K65R substitution, outweighs the risk that individuals may become infected during a period of interruption.

In addition, we expect that this temporary discontinuation in therapy will prompt physicians to recommend use of barrier methods or temporary abstinence while individuals await their test results. As individuals with acute infection may be more likely to transmit infection, use of barrier methods or sexual abstinence during this period may decrease the likelihood that these individuals will transmit to their partners.

In summary, we advise that the Section 5.9 of the TRUVADA labeling remain as it currently reads.

§ While using TRUVADA for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Warm Regards,  
Katie

Katherine Schumann, M.S.  
Regulatory Project Manager

FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: [Katherine.Schumann@fda.hhs.gov](mailto:Katherine.Schumann@fda.hhs.gov)

---

**From:** Dara Wambach [mailto:Dara.Wambach@gilead.com]  
**Sent:** Tuesday, July 10, 2012 1:17 PM  
**To:** Schumann, Katherine  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** NDA 21-752-S-30 - Proposed Alternative Text to Section 5.9 in Truvada PI

**RE: NDA 21-752-S-30 - Proposed Alternative Text to Section 5.9 in Truvada PI**

Dear Katie,

As just discussed via phone, Gilead has one final proposed change to the labeling for Truvada in Section 5.9; this change arose after the teleconference yesterday, so is not included in the labeling sent via email prior to the meeting. Please find attached a draft response document illustrating the proposed revision. We appreciate very much your taking this to the DAVP review team for consideration.

Kind regards,  
Dara

Dara Wambach, MA  
Associate Director, Regulatory Affairs  
Gilead Sciences  
ph: 650-522-5163

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/s/  
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KATHERINE SCHUMANN  
07/15/2012

**From:** [Schumann, Katherine](#)  
**To:** ["Dara Wambach"](#)  
**Cc:** [Regulatory Archives](#)  
**Subject:** NDA 21752 S-030 - TRUVADA labeling comment  
**Date:** Monday, July 09, 2012 3:05:00 PM

---

Dear Dara,

Please find below one comment on the TRUVADA labeling (Section 6.2):

*Laboratory Abnormalities:* Table 5 provides a list of laboratory abnormalities observed in both trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued participation in the study due to an increase in blood creatinine compared with no discontinuations in the placebo group. One subject in the TRUVADA arm of the iPrEx trial discontinued from the study due to an increase in blood creatinine **and another due to low phosphorus.** [REDACTED] (b) (4)

This new text refers to Subject 9433750 in the iPrEx trial who permanently discontinued study drug due to recurrent hypophosphatemia and persistent glycosuria, per the datasets and CRFs.

We can discuss further during our teleconference this afternoon, if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993  
Tel: 301-796-1182  
Fax: 301-796-9883  
Email: [Katherine.Schumann@fda.hhs.gov](mailto:Katherine.Schumann@fda.hhs.gov)

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/s/  
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KATHERINE SCHUMANN  
07/15/2012

**From:** [Schumann, Katherine](#)  
**To:** ["Dara Wambach"](#)  
**Cc:** [Regulatory Archives](#)  
**Subject:** Re: NDA 21752 S-030 TRUVADA REMS website questions  
**Date:** Monday, July 09, 2012 1:44:00 PM

---

Dear Dara,

Please find below your questions regarding the REMS website followed by answers from DRISK, in blue. If you have any further questions, we can discuss them during the teleconference later today. Thanks, Katie.

### Questions

[REDACTED] (b) (4)

1) We appreciated receiving the website comments in advance from the Agency; the permanent website is being finalized as rapidly as possible. [REDACTED] (b) (4)

[REDACTED]

While several of the details included in the original proposal are now out of date, the intention remains, with a landing page that will support download of the Full Prescribing Information and Medication Guide and all the REMS materials as PDF files.

1a. We would like to please seek the Agency's confirmation on this plan and guidance on submission of the landing page in advance of approval. Gilead proposes to submit a copy of [REDACTED] (b) (4) during the week of 09 July 2012. **The Agency concurs with this plan. Please note, materials on the landing page (and all subsequent pages) must be revised to be consistent with the final FDA-approved labeling.**

**1b. In follow-up, this question relates to [REDACTED] (b) (4) and permanent REMS website: is the [REDACTED] (b) (4) intended to be available on the website? We note that [REDACTED] (b) (4) is identical in content to the Safety Information Fact Sheet and not currently listed as part of the Educational Kit with components listed in the REMS Document. The [REDACTED] (b) (4) is identical in content to the Safety Information Fact Sheet and not currently listed as part of the educational kit in the REMS document; therefore, the Agency recommends removing the [REDACTED] (b) (4) from the REMS website.**

### Option for Collection of HCP Specialty and Degree

2) We noted and seek clarification regarding the Agency's comments on Page 17 - 32 of the website, that requests removal of the 'assess your knowledge' link. The 'asses your knowledge' leads to the training assessment questions followed by a page from which [REDACTED] (b) (4). Based upon this comment, it is understood that [REDACTED] (b) (4) should be omitted from the website, but we are not certain about the role of the assessment questions.

In addition, Gilead proposes to maintain a query to collect data on healthcare provider specialty and degree via a simplified drop-down menu. This would support collection of this information directly and at the time that the HCP has engaged with the REMS training and help address a component of the required REMS assessment.

2a) Could the Agency please clarify if the assessment questions should be removed from the website?

2b) Does the Agency agree with the collection of HCP specialty and degree via drop-down menus on the REMS website, either following the assessment or at another location on the REMS website?

The Agency was under the assumption that Gilead was referring to the KAB surveys when referencing the (b) (4)"; therefore we would like to retract our comments regarding the (b) (4) sent on Friday, July 6 and provide the following:

The questions can remain on the REMS website. However, starting on page 2 of the REMS website, and all subsequent pages where there is reference to (b) (4)" remove these terms and replace with "Post-training Review Questions".

In addition, the Agency agrees with the collection of HCP specialty and degree via drop-down menus on the REMS website, following the post-training review questions on the REMS website.

#### **Response to Request for Information**

We also have a reply related to a request for clarification provided in the Agency's comments of 05 July 2012 pertaining to pages 3 - 16. Healthcare Provider Training "slides" appear over another page with other content. Clarify how this will look in the final REMS website.

Please find below a few points and a screenshot illustrating the view attached.

- The content that appears in the overlay (pop-up) for the prescriber training/assessment will never hide content from the user
- The content in the grey area of the background is fully visible before the overlay is opened
- At any time, a user can close the overlay by clicking the 'X' which will return the user to the original page

**Thank you for your clarification.**

---

**From:** Dara Wambach [mailto:Dara.Wambach@gilead.com]  
**Sent:** Sunday, July 08, 2012 11:00 PM  
**To:** Schumann, Katherine  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** RE: NDA 21752 S-030 TRUVADA REMS website questions

**RE: NDA 21752 S-030 TRUVADA REMS website questions**

Dear Katie,

On Friday, I mentioned that we had a few questions regarding the website. The questions are as

follows:

### **Questions**

[REDACTED] (b) (4)

1) We appreciated receiving the website comments in advance from the Agency; the permanent website is being finalized as rapidly as possible. [REDACTED] (b) (4)

[REDACTED] While several of the details included in the original proposal are now out of date, the intention remains, with a landing page that will support download of the Full Prescribing Information and Medication Guide and all the REMS materials as PDF files.

**1a. We would like to please seek the Agency's confirmation on this plan and guidance on submission of the landing page in advance of approval. Gilead proposes to submit a copy of [REDACTED] (b) (4) during the week of 09 July 2012.**

**1b. In follow-up, this question relates to [REDACTED] (b) (4) permanent REMS website: is the [REDACTED] (b) (4) intended to be available on the website?** We note that the [REDACTED] (b) (4) is identical in content to the Safety Information Fact Sheet and not currently listed as part of the Educational Kit with components listed in the REMS Document.

#### Option for Collection of HCP Specialty and Degree

2) We noted and seek clarification regarding the Agency's comments on Page 17 - 32 of the website, that requests removal of the 'assess your knowledge' link. The 'assesses your knowledge' leads to the training assessment questions followed by a page from which [REDACTED] (b) (4). Based upon this comment, it is understood that [REDACTED] (b) (4) should be omitted from the website, but we are not certain about the role of the assessment questions.

In addition, Gilead proposes to maintain a query to collect data on healthcare provider specialty and degree via a simplified drop-down menu. This would support collection of this information directly and at the time that the HCP has engaged with the REMS training and help address a component of the required REMS assessment.

**2a) Could the Agency please clarify if the assessment questions should be removed from the website?**

**2b) Does the Agency agree with the collection of HCP specialty and degree via drop-down menus on the REMS website, either following the assessment or at another location on the REMS website?**

### **Response to Request for Information**

We also have a reply related to a request for clarification provided in the Agency's comments of 05 July 2012 pertaining to pages 3 - 16. **Healthcare Provider Training "slides" appear over another page with other content. Clarify how this will look in the final REMS website.**

Please find below a few points and a screenshot illustrating the view attached.

- The content that appears in the overlay (pop-up) for the prescriber training/assessment will never hide content from the user
- The content in the grey area of the background is fully visible before the overlay is opened
- At any time, a user can close the overlay by clicking the 'X' which will return the user to the

original page

We appreciate the opportunity to clarify and seek clarification on these issues on a rapid basis as we finalize the REMS materials. Verbal and/or written responses to these questions are welcome and will be incorporated immediately into the website development.

Kind regards,  
Dara

Dara Wambach, MA  
Associate Director, Regulatory Affairs  
Gilead Sciences  
333 Lakeside Drive  
Foster City, CA 94404  
ph: 650-522-5163  
cell: 415-710-1725

---

**From:** Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]  
**Sent:** Thursday, July 05, 2012 2:33 PM  
**To:** Dara Wambach  
**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-030 TRUVADA REMS website comments

Dear Dara,

Given that the REMS website takes the most time to revise of all of the REMS materials, DRISK/DAVP are sending you the following comments on the TRUVADA REMS website prior to sending comments on the rest of the REMS materials. Those additional REMS comments will be sent tomorrow (July 6). The comments below pertain to the REMS website PDF submitted on July 3, 2012 and received on July 5, 2012.

Please re-submit the website to the sNDA with these revisions as soon as possible:

### Pages 1 - 16

- Remove  (b) (4)
- Clarify what information and/or materials are included in the link entitled, "Access REMS resources" to the right of the page contents

### Pages 3 - 16

- Healthcare Provider Training "slides" appear over another page with other content. Clarify how this will look in the final REMS website.

### Page 17 - 32

- The applicant refers HCPs to "assess your knowledge" and provides what appears to be a link to an assessment for prescriber knowledge. Per previous conversations with the applicant, the DRISK required that all referrals and/or links to the assessment be removed from the REMS website. It is the Agency's recommendation that a recruitment

communication from the applicant or a vendor be sent to prescribers and uninfected individuals via a separate internet link or by printed copy for access to the respective KAB surveys. We refer you to our comments dated April 26, 2012

### **Pages 17- 37**

- Remove the "assess your knowledge" link in the tool bar at the top of these pages

### **Page 22**

- Remove [REDACTED] (b) (4) at the top of this page and replace it with REMS MATERIALS. Remove REMS MATERIALS above the Dear Healthcare Provider Letter

### **Page 33**

- Page 33, remove the prompt to [REDACTED] (b) (4)

### **Page 36**

- "Assess Your Knowledge" link at the bottom of the page must be removed

The REMS webpage should stop at the end of page 36

### **Page 37**

- Page 37 - [REDACTED] (b) (4) message should be deleted

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993  
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/s/  
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KATHERINE SCHUMANN  
07/15/2012

**From:** Schumann, Katherine  
**To:** ["Dara Wambach"](#)  
**Cc:** [Regulatory Archives](#)  
**Subject:** NDA 21752 S-030 Labeling request regarding [REDACTED] (b) (4)  
**Date:** Monday, July 09, 2012 6:22:00 PM

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Dear Dara,

After consultation with the review team, DAVP requests that Gilead **not** add a recommendation to the TRUVADA labeling stating that [REDACTED] (b) (4)

Please let me know if you or your colleagues have any questions.

Warm Regards,

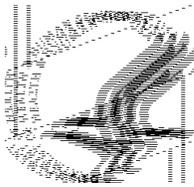
Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
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/s/  
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KATHERINE SCHUMANN  
07/15/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** July 6, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Additional REMS Comments

---

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/tenofovir disoproxil fumarate) tablets. Please also refer to your submissions of July 2, 2012 and July 3, 2012, containing the revised proposed REMS for Truvada.

The following are requested revisions to the Amendments to the proposed REMS for TRUVADA (received on July 3 and 5, 2012, respectively). Please submit your responses to these comments to the Agency by close of business July 12, 2012. If this is not possible, notify the Agency as soon as possible as to the expected submission date of these revised materials.

Comprehension Testing of REMS Training and Educational Materials

The DRISK clarifies for the applicant that comprehension testing with the target audience for each REMS Training and Educational material (including the Medication Guide) is required by the Agency. We recommend the following target audiences:

- Uninfected individuals taking TRUVADA for a PrEP indication *and* patients taking TRUVADA for treatment of HIV disease should be included in comprehension testing of the Medication Guide
- Prescribers across primary care (internal medicine, family practice, and general medicine) and specialists (Infectious Disease, Obstetricians-gynecologists and Addiction) should be included in comprehension testing of all of the prescriber training and educational materials

## REMS Supporting Document

1. The DRISK clarifies for the applicant that the revisions to use the word “provider” instead of [REDACTED] (b) (4) in the REMS Supporting Document are acceptable to the Agency.
2. The DAVP and the DRISK request that the REMS Supporting Document be edited to use the word, “substitution” instead of [REDACTED] (b) (4). See the following sections of the REMS Supporting Document:
  - a. Section 1.1 Overview:
    - On page 4, last paragraph, delete “[REDACTED] (b) (4)” and insert “amino acid substitution”
  - b. Section 1.1.2 Identified Risk of Development of Resistance:
    - On page 7, delete [REDACTED] (b) (4) and insert “substitutions”
  - c. Section 2.4.3 Key Risk Messages see Table 2. Risk Evaluation and Mitigation Strategy Summary:
    - On page 20, delete [REDACTED] (b) (4),” and insert “substitution”

## Prescriber Educational Slide Deck

Slide 2 - Remove [REDACTED] (b) (4). Place emtricitabine and tenofovir disoproxil fumarate in parentheses immediately after TRUVADA, as is done in the TRUVADA package insert.

Slide 4, bullet 3 - Update HIV testing language. Revise bullet 3 to state, "...as demonstrated by measurable drug levels in a subgroup of clinical trials subjects". Revise bullet 4 to state, "Screen individuals for..."

Slide 5 - Switch the words “use” and “the” in 5<sup>th</sup> line. Add "...until negative infection status is confirmed"

Slide 6 - Add recommendation for hepatitis B screening and vaccination of susceptible individuals.

Slide 7 - Revise to "Missing doses may increase the risk of acquiring HIV"

Slide 8 - Revise to be consistent with prescriber training materials

- In one clinical trial of TRUVADA for a PrEP indication, TRUVADA was shown to reduce the risk of HIV-1 acquisition by 42% for high risk men who have sex with men who also received comprehensive prevention services, including monthly HIV-1 testing, condom provision, counseling, and management of other sexually transmitted infections

- In a post hoc case control study of plasma and intracellular drug levels in about 10% of clinical trial subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence

The phrase "self-reported" should precede sexual partners in the third bullet point.

Slide 9 - Add heterosexual to description of serodiscordant couples

Slide 12 - update all HIV testing language (both for initiation of PrEP and while using PrEP)

Slide 13 - Revise statement as follows, "...as demonstrated by measurable drug levels in a subgroup of clinical trials subjects"

Slide 14 - update last sentence regarding use of Truvada in uninfected individuals with a decrease in CrCl (add "potential risks and benefits" language)

Slide 19 - Revise adverse event description to be consistent with package insert

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Attachments:

- REMS Document
- Safety Information Fact Sheet
- Journal Information Piece
- Dear Healthcare Provider Letter
- Important Safety Information about TRUVADA for a PrEP indication for Healthcare Providers
- Important Safety Information about TRUVADA for a PrEP indication for Uninfected Individuals
- Training Guide for Healthcare Providers
- Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis (PrEP) of Sexually Acquired HIV-1 Infection
- Checklist for Prescribers: Initiation of TRUVADA for PrEP

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/s/  
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KATHERINE SCHUMANN  
07/06/2012

**From:** [Schumann, Katherine](#)  
**To:** [Dara Wambach](#);  
**cc:** [Regulatory Archives](#);  
**Subject:** NDA 21752 S-030 TRUVADA REMS website comments  
**Date:** Thursday, July 05, 2012 5:32:00 PM

---

Dear Dara,

Given that the REMS website takes the most time to revise of all of the REMS materials, DRISK/DAVP are sending you the following comments on the TRUVADA REMS website prior to sending comments on the rest of the REMS materials. Those additional REMS comments will be sent tomorrow (July 6). The comments below pertain to the REMS website PDF submitted on July 3, 2012 and received on July 5, 2012.

Please re-submit the website to the sNDA with these revisions as soon as possible:

### **Pages 1 - 16**

Remove

(b) (4)

Clarify what information and/or materials are included in the link entitled, "Access REMS resources" to the right of the page contents

### **Pages 3 - 16**

Healthcare Provider Training "slides" appear over another page with other content. Clarify how this will look in the final REMS website.

### **Page 17 - 32**

The applicant refers HCPs to "assess your knowledge" and provides what appears to be a link to an assessment for

prescriber knowledge. Per previous conversations with the applicant, the DRISK required that all referrals and/or links to the assessment be removed from the REMS website. It is the Agency's recommendation that a recruitment communication from the applicant or a vendor be sent to prescribers and uninfected individuals via a separate internet link or by printed copy for access to the respective KAB surveys. We refer you to our comments dated April 26, 2012

### **Pages 17- 37**

Remove the "assess your knowledge" link in the tool bar at the top of these pages

### **Page 22**

Remove  (b) (4) at the top of this page and replace it with REMS MATERIALS. Remove REMS MATERIALS above the Dear Healthcare Provider Letter

### **Page 33**

Page 33, remove the prompt to  (b) (4)  


### **Page 36**

"Assess Your Knowledge" link at the bottom of the page must be removed

The REMS webpage should stop at the end of page 36

### **Page 37**

Page 37 -  (b) (4)" message should be

deleted

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993  
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/s/  
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KATHERINE SCHUMANN  
07/05/2012

**From:** [Schumann, Katherine](#)  
**To:** [Dara Wambach](#);  
**cc:** [Regulatory Archives](#);  
**Subject:** NDA 21752 S-30 Final Med Guide Comments  
**Date:** Thursday, July 05, 2012 11:33:00 AM  
**Attachments:** 7-2-12 DMPP MG edits\_June 29 draft-labeling-tracked.doc

---

Dear Dara,

Please find attached the TRUVADA labeling with final, minor comments on the Medication Guide. Please disregard the full prescribing information before the Med Guide, as the PI does not contain our most recent set of changes.

Let me know if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.  
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FDA/CDER/OND/OAP  
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KATHERINE SCHUMANN  
07/05/2012

**From:** [Schumann, Katherine](#)  
**To:** ["Dara Wambach";](#)  
**cc:** [Regulatory Archives;](#)  
**Subject:** NDA 21752 S-30 Comment Regarding Resistance PMR  
**Date:** Tuesday, July 03, 2012 8:53:00 AM

---

Dear Dara,

In response to your PMR/PMC response submitted last Thursday, June 28 to NDA 21752 S-030, the clinical virology team has the following comment regarding PMR #1:

We recommend the use of ultrasensitive tests for proviral DNA over viral RNA due to concerns that the proportion of resistant variants will diminish to undetectable levels more rapidly for the viral population than for that of proviruses. This might be particularly likely for individuals who are intermittently compliant, are tested for seroconversion infrequently, and who harbor resistant variants that are markedly less fit than wild-type virus. We acknowledge that the necessary samples may not be made available to you for such analyses. However, please include the ultrasensitive genotypic analysis of the proviral DNA when feasible, particularly for seroconverters without detectable levels of genotypic resistance by the population or allele-specific analyses.

Warm Regards,

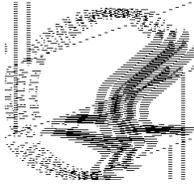
Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
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/s/  
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KATHERINE SCHUMANN  
07/03/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** July 3, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – PMR/PMC Correspondence

---

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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of June 28, 2012, containing revised PMRs and PMCs.

Please find attached the Division's revised PMRs and additional proposed PMCs for NDA 21752 S-030.

PMR #1 has been edited to incorporate appropriate FDAAA language.

PMR #2 has been edited to incorporate appropriate FDAAA language. In addition, a third control group has been added to the PMR. We believe the most appropriate comparator group for pregnant women continuing Truvada throughout pregnancy will be the group of women using Truvada for the purposes of conception and electing to discontinue Truvada once pregnancy is confirmed. This will provide important comparative data on rates of HIV seroconversion, pre-term deliveries and other outcomes. As described in the attached article on pregnancy outcomes in the May 2012 issue of CID, pregnancy outcomes such as pre-term deliveries may be impacted by type of ARV used during pregnancy, making a comparator group of HIV-infected women receiving other ARV regimens during pregnancy of limited value.

In addition to the revised PMRs, we are sending you two proposals for additional PMCs. Your currently proposed demonstration project, with appropriate modifications, could be used to fulfill these.

Please provide a response to the PMR revisions by Thursday, July 5, 2012 and proposals for additional PMCs by Friday, July 6, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Attachments:

- Revised PMRs
- Additional Proposed PMCs:
  - Outline of General Advice Letter for Observational Study
  - PMC Adherence Study Request
- Sibiude J, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis. 2012 May;54(9):1348-60. Epub 2012 Mar 28.

## Revised PMRs

1) Collect and analyze data from individuals participating in demonstration projects (trials) who seroconvert during follow-up. The following data should be collected over a time period not to exceed 3 years and to be completed when data are collected and analyzed from a minimum of 150 seroconverters enrolled in demonstration projects (trials):

- a. Data regarding the presence or absence of signs and symptoms of acute HIV infection at the trial visit or since the last trial 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 for 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 ultradeep sequencing of proviral DNA or allele-specific PCR) if no resistance is identified by population sequencing.

Timeline:      Final protocol submission – Oct 2012  
                    Interim report submissions –Sept 2013, Sept 2014, Sept 2015  
                    Final report submission – Sept 2016

2) 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 pre-exposure prophylaxis (PrEP) 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 mother 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.

Timeline:      Final protocol submission – Oct 2012  
                    Study completion – (b) (4)  
                    Final report submission – (b) (4)

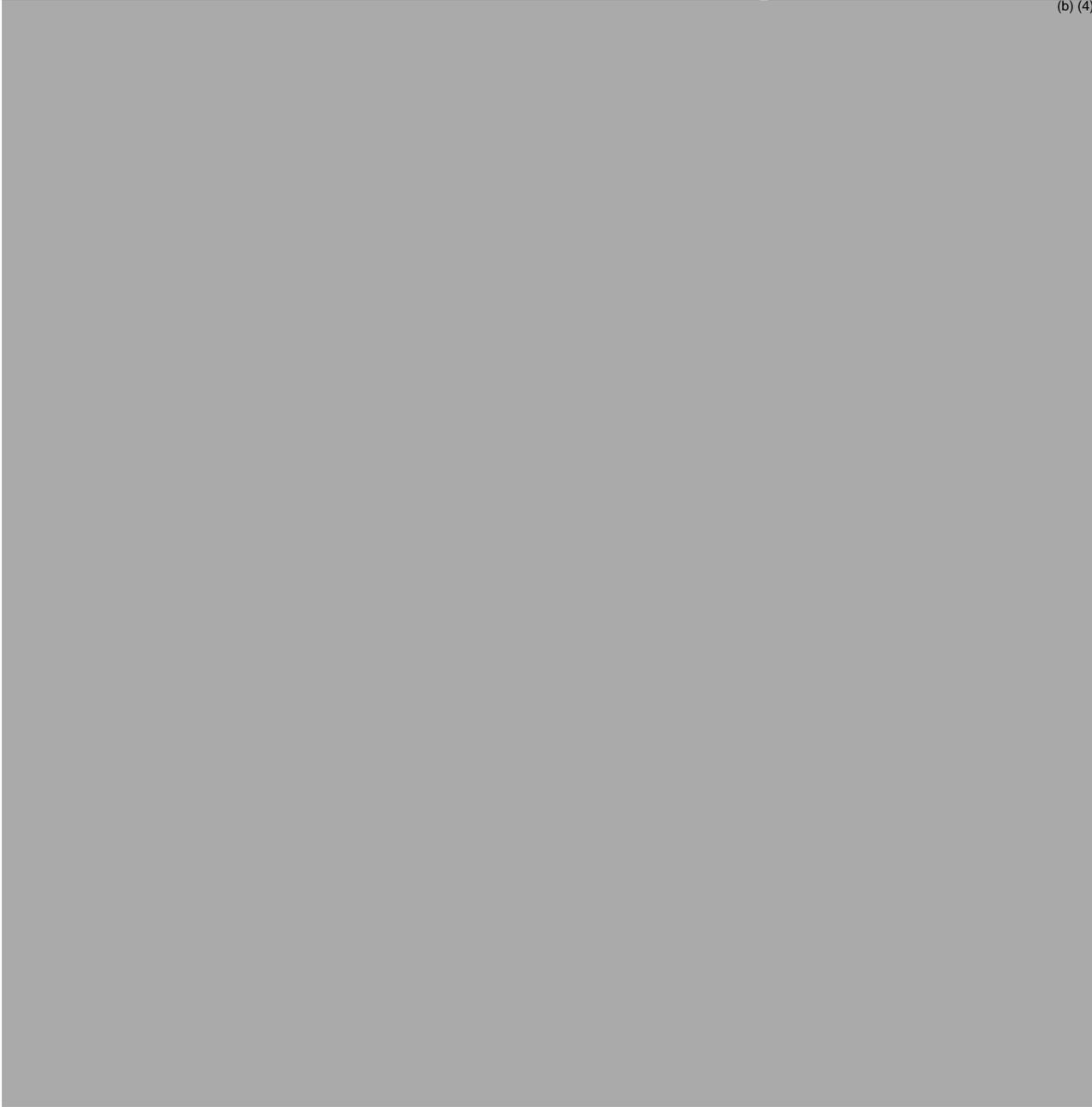
### Outline of General Advice Letter for Observational Study

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Truvada® (200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) tablets and your Investigational New Drug Application for Truvada® tablets.

We also refer to your June 25, 2012, submission containing the draft observational protocol “The Gilead Pre-Exposure Prophylaxis (PrEP) Registry of Uninfected Individuals Taking Truvada® as Part of a Comprehensive HIV Prevention Strategy,” submitted under sNDA 21752 / S-030.

We have reviewed the referenced material and have the following comments:

(b) (4)



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## POST-MARKETING COMMITMENT REQUEST

Post-marketing commitment: Conduct a prospective observational uncontrolled study with the objective of examining the association between levels of adherence to once-daily Truvada® prescribed for pre-exposure prophylaxis and risk of seroconversions, resistance, 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.’ Assessment of seroconversion should be assessed every three months, and, upon each seroconversion, assessment of resistance testing should be performed. Assessment for renal and skeletal adverse events should include lab work (such as urinalysis) performed every three months. Effect of adherence on effectiveness and safety of Truvada® should be put into the context of sexual and non-sexual patient behaviors that may affect the risk of HIV infection.

A patient survey administered by healthcare providers may be used as the primary instrument for measuring adherence contingent on the following:

- The survey has been validated in a national demographically representative sample that reflects the target population of HIV-negative patients in the United States who are at high risk of sexually-acquired HIV-1 infection, and on once-daily Truvada® for the indication of HIV pre-exposure prophylaxis.
- The survey is highly sensitive for the detection of non-adherence and moderately to highly specific for the detection of adherence.
- The survey has concurrent criterion validity for long-term adherence. Specifically, the detection of non-adherence concurs with long-term adherence as measured by an objective biological measure(s), such as intracellular tenofovir-diphosphate or emtricitabine / tenofovir in scalp hair. (Note that, at this time, the validity of scalp hair to predict long-term adherence to Truvada® is currently not demonstrated and an additional pharmacokinetic study will be required prior to use of this measure as a criterion for long-term adherence.)

Other aspects of the prospective observational study should, as much as possible, reflect real-world clinical care.

Post-marketing commitment: Validate a survey on patient knowledge, attitudes, and behaviors that predicts future adherence to once-daily Truvada® for pre-exposure prophylaxis. The survey should be validated in a national demographically representative sample that reflects the same target population as described above.

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/s/  
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KATHERINE SCHUMANN  
07/03/2012

**From:** [Schumann, Katherine](#)  
**To:** ["Dara Wambach"](#);  
**cc:** [Regulatory Archives](#); [Paul Tomkins](#);  
**Subject:** RE: NDA 21-752/S-030 - Query re HIV tests capable of detecting acute infection  
**Date:** Thursday, June 28, 2012 5:14:00 PM

---

Dear Dara,

The Division has considered your request below regarding the labeling for TRUVADA. Although we are not comfortable with the specific recommendation of (b) (4), there may be acceptable alternative wording that will address your concerns below. The Division proposes the following change:

(b) (4)

to

(b) (4)

We look forward to receiving the revised labeling for review.

Warm Regards,

Katie  
301-796-1182

---

**From:** Dara Wambach [mailto:Dara.Wambach@gilead.com]  
**Sent:** Thursday, June 28, 2012 12:14 AM  
**To:** Schumann, Katherine  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** NDA 21-752/S-030 - Query re HIV tests capable of detecting acute infection

**RE: NDA 21-752/S-030 - Query re HIV tests capable of detecting acute infection**

Dear Katie,

Thank you very much for gathering your team for the labeling discussion today; we are progressing the labeling based upon the outcome reached today. In the meantime, we have one additional point for consideration.

(b) (4)





Kind regards,  
Dara

Dara Wambach, MA  
Associate Director, Regulatory Affairs  
Gilead Sciences  
333 Lakeside Drive  
Foster City, CA 94404  
Ph: 650-522-5163  
Fax: 650-522-5489  
Email: [dara.wambach@gilead.com](mailto:dara.wambach@gilead.com)

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/s/  
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KATHERINE SCHUMANN  
06/28/2012

## Schumann, Katherine

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**From:** Schumann, Katherine  
**Sent:** Tuesday, June 26, 2012 4:22 PM  
**To:** Schumann, Katherine; 'Dara Wambach'  
**Cc:** 'Regulatory Archives'  
**Subject:** RE: NDA 21752 S-030 TRUVADA REMS Comments - Corrections and Additional Comments

**Attachments:** 6-14-12 dear-healthcare-provider-letter (2) (3).rtf; 6-14-12 training-guide-for-hcps-clean.pdf

Dear Dara,

Please note that two of the attached REMS materials sent this morning need to be replaced. I have attached corrected versions of the following:

Dear Healthcare Provider Letter (dated 6/14/12)  
Training Guide for Healthcare Providers (dated 6/14/12)

Please delete the versions sent this morning, dated 5/22/12.

I also have two additional comments from DRISK regarding the REMS materials that we would like you to address:

1. On page 3 of the Training Guide for Healthcare Providers (page 2 of the PDF), under the heading "The iPrEx study", the first bullet should state "an average 42% protection" instead of "an average (b) (4) % protection". Please see the change in blue below.

In one clinical study of TRUVADA for a PrEP indication, TRUVADA provided an average 42% protection to men who have sex with men who also received comprehensive prevention services, including monthly HIV testing, condom provision, counseling, and management of other sexually transmitted infections

2. On page 4 of the Important Safety Information for Uninfected Individuals (Page 3 of the PDF), please add "you must" after the words "That is why:" and remove "you must" from all of the individuals bullets. Please see the changes below (additional wording in blue, delted wording in strikethrough). Note that the word "must" should be bolded.

### Starting TRUVADA for a PrEP Indication

#### Before starting TRUVADA for a PrEP indication

You must be HIV-1 negative and stay HIV-1 negative **before** starting TRUVADA for a PrEP indication. That is why **you must**:

- ~~You must~~ **Get** tested to be sure you do not have HIV-1 and be retested regularly (at least every 3 months)
- ~~You must~~ **Have** no HIV-1 symptoms, such as feeling tired, fever, sweating, pain, rash, diarrhea, or cough
- ~~You must~~ **Know** whether or not you have hepatitis B
- ~~You must~~ **Be** prepared to commit to adopting safer sex practices, such as regular and correct use of condoms, limiting your number of sexual partners, and regular testing for HIV-1 (at least every 3 months) and other sexually transmitted infections, such as syphilis and gonorrhea
- ~~You must~~ **Make** certain you understand the risks and benefits of taking TRUVADA for a PrEP indication as outlined in the TRUVADA Medication Guide and in the Prescriber-Individual Agreement, and you have spoken with your healthcare provider about questions and concerns

Please let me know if you have any questions.

Warm Regards,

Katie  
301-796-1182



6-14-12



6-14-12

ar-healthcare-provoining-guide-for-hcp

---

**From:** Schumann, Katherine  
**Sent:** Tuesday, June 26, 2012 10:51 AM  
**To:** 'Dara Wambach'  
**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-030 TRUVADA REMS Comments

Dear Dara,

Please find attached a correspondence containing comments from DAVP and DRISK on the proposed REMS for Truvada. I am also attaching each of the appended REMS materials as separate documents for your convenience (some in MS Word).

On a related note, I received several additional comments on the TRUVADA prescribing information from OPDP (DDMAC) yesterday afternoon that I will be sending to you later today. Please incorporate them into your current round of labeling revisions. I will specify in the communication that we won't expect the labeling until Friday (unless you believe Thursday is still feasible).

Thanks and Warm Regards,

Katie

<< File: 2012\_06\_26 NDA 21752 S-30 REMS Comments.pdf >>

<< File: 06-25-12 Proposed REMS TRUVADA-clean.doc >> << File: 6-14-12 safety-information-fact-sheet.pdf >> << File: 6-14-12 journal-information-piece.pdf >> << File: 5-22-12 Dear Healthcare Provider.doc >> << File: 6-14-12 prescriber-safety-brochure.pdf >> << File: 6-14-12 individual-safety-brochure.pdf >> << File: 5-22-12 training-guide-for-hcps-clean.pdf >> << File: 06-18-12 prescriber-individual-agreement-form.doc >> << File: 06-21-12 Checklist-for-prescribers.doc >> << File: 6-14-12 truvada-rems-website.pdf >>

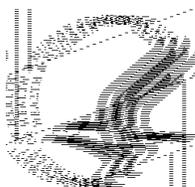
Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993  
Tel: 301-796-1182  
Fax: 301-796-9883  
Email: Katherine.Schumann@fda.hhs.gov

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/s/  
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KATHERINE SCHUMANN  
06/26/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-030

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets

**Date:** June 26, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-030 Truvada for a PrEP indication – Additional Comments Regarding Proposed Labeling

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of June 21, 2012, containing revised labeling for TRUVADA.

The attached comments regarding the proposed TRUVADA prescribing information are being communicated to you on behalf of DAVP and OPDP.

Given that we are sending these revisions in addition to the comments sent on June 25, 2012, we will not expect to receive your response to either request until Friday, June 29, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Enclosed: Draft Prescribing Information

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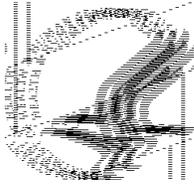
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/s/

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KATHERINE SCHUMANN  
06/26/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** June 26, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Additional REMS Comments

---

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/tenofovir disoproxil fumarate) tablets. Please also refer to your submissions of June 4, June 13 and June 18, containing the revised proposed REMS for Truvada.

The following are required revisions to the Amendments (sNDA 21-752/Supplement 30/Sequence 745, 748 and 749) to the proposed REMS for TRUVADA for a PrEP Indication (received on June 5, 14, and 19, 2012, respectively) that must be completed for the REMS to be acceptable to the Agency. The Agency requests that responses to these comments and required revisions be submitted to the Agency by close of business on July 2, 2012. If this is not possible, notify the Agency as soon as possible as to the expected submission date of these revised materials.

**Proposed REMS**

See **Attachments:** REMS Document (clean version is acceptable to the Agency)

1. GOALS: The goals, as amended, are acceptable to the Agency.
2. REMS Elements:
  - a. Medication Guide comments on the Medication Guide will be provided under separate communication from the Agency.
  - b. Element to Assure Safe Use (ETASU): Prescriber Training and Education  
Incorporate the required track changes in the appended REMS training and

educational materials to reflect revisions to the Full Prescribing Information. See **Attachments** with track changes in the following materials:

- i. Safety Information Fact Sheet
- ii. Dear Healthcare Provider letter
- iii. Important Safety Information about TRUVADA for a PrEP Indication for Healthcare Providers
- iv. Important Safety Information about TRUVADA for a PrEP Indication for Uninfected Individuals
- v. Training Guide for Healthcare Providers
- vi. Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis (PrEP) of Sexually Acquired HIV-1 Infection
- vii. Checklist for Prescribers: Initiation of TRUVADA for PrEP
- viii. REMS program website, [www.truvadapreprems.com](http://www.truvadapreprems.com)
- ix. Journal Information Piece

Comments on the Prescriber Educational Slide Deck were sent to you in an Information Request letter (dated June 20, 2012) from the Agency.

### 3. Timetable for Submission of Assessments

The Timetable for Submission of Assessments, as amended, is acceptable to the Agency.

### **REMS Assessment**

Additional reports are required in the REMS Assessment to be acceptable to the Agency. Add the following reports to the REMS Assessment:

1. Prescribers, by specialty type, who prescribe Truvada for a PrEP indication to the extent possible
2. Drug resistance in negative HIV-1 individuals who seroconvert to positive HIV-1 during use of Truvada as monotherapy, to the extent possible
3. Compliance with regular HIV-1 testing (at least every 3 months) in individuals using Truvada for a PrEP indication, to the extent possible
4. Comprehension testing of the REMS educational and training materials to be included in the 6-month REMS assessment
5. With respect to any post approval clinical trial required under Section 505(0) or otherwise undertaken to investigate a safety issue, the following will be included:
  - a. The status of such clinical trial, including whether or not enrollment has begun, and the number of participants enrolled
  - b. The expected completion date, whether any difficulties completing the clinical trial have been encountered

- c. Registration information with respect to requirements under subsections (i) and (j) of Section 402 of the Public Health Service Act

**REMS Supporting Document**

Please revise the REMS Supporting Document to be consistent with all changes made to the REMS Document, training and educational materials and REMS assessment.

**Resubmission Instructions**

- Submit the amendment to the REMS proposed for TRUVADA for a PrEP indication with all of the appended REMS materials, the REMS website landing page and subsequent screen shots, and the REMS Supporting Document.
- Provide a MS Word document with track changes and a clean MS Word version of all (each) revised material and document.
- Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

**Format Request:**

Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the documents 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as the REMS website landing page are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single MS Word document.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Attachments:

- REMS Document
- Safety Information Fact Sheet
- Journal Information Piece
- Dear Healthcare Provider Letter
- Important Safety Information about TRUVADA for a PrEP indication for Healthcare Providers
- Important Safety Information about TRUVADA for a PrEP indication for Uninfected Individuals
- Training Guide for Healthcare Providers
- Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis (PrEP) of Sexually Acquired HIV-1 Infection
- Checklist for Prescribers: Initiation of TRUVADA for PrEP

- REMS program website, [www.truvadapreprems.com](http://www.truvadapreprems.com)

Initial REMS Approval: xx/xx/2012

**Supplemental NDA 21-752**

**TRUVADA<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate)**

Nucleoside /Nucleotide Analog Human Immunodeficiency Virus-1

Reverse Transcriptase Inhibitors

**Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOALS**

The goals of the REMS for TRUVADA for a Pre-Exposure Prophylaxis (PrEP) Indication are:

To 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 regular 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
- The fact that TRUVADA for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

## II. REMS ELEMENTS

### A. Medication Guide

A TRUVADA Medication Guide will be dispensed with each TRUVADA prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

### B. Elements to Assure Safe Use

1. Gilead Sciences, Inc, will ensure that training and education through the TRUVADA for a PrEP Indication Healthcare Professional Education Program is available to healthcare prescribers who prescribe TRUVADA for a PrEP indication.
  - a. Gilead will ensure that training and education materials will be available for completion by healthcare prescribers who prescribe TRUVADA for a PrEP indication via the TRUVADA for a PrEP Indication Healthcare Professional Education Program online via the REMS Website ([www.truvadapreprems.com](http://www.truvadapreprems.com)) or by print training modules available as hard copy, upon request. This information will remain on the REMS website for a period of 3 years from initial approval.
  - b. Gilead's training efforts will target the following healthcare prescribers who are likely to prescribe TRUVADA for a PrEP indication:
    - Primary care physicians, including internal medicine, family practice, and general medicine physicians
    - Infectious Diseases specialists
    - Obstetrician-gynecologists
    - Addiction specialists
  - c. In order to facilitate prescriber training and education, Gilead will disseminate information about the potential and known safety risks with TRUVADA for a PrEP indication to select professional organizations for outreach to healthcare prescribers likely to prescribe TRUVADA for a PrEP indication as described in b. above.
    - i. The Safety Information Fact Sheet will be available for distribution via online access or printed hard copy for select professional organizations to disseminate to healthcare prescribers bi-annually, for 3 years.
    - ii. The Safety Information Fact Sheet will include:

- The importance of strict adherence to the recommended dosing regimen
  - The importance of regular 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
  - The fact that TRUVADA for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used
- iii. Within 60 days of product approval or at the time of product launch, whichever is sooner, and again at 6, 12, and 24 months, Gilead will send the Safety Information Fact Sheet to the following professional organizations:
- HIV Medicine Association/Infectious Diseases Society of America
  - American Academy of HIV Medicine
  - Association of Nurses in AIDS Care
  - National Medical Association
  - American Academy of Family Physicians
  - American Society of Addiction Medicine
  - American College of Obstetricians and Gynecologists
  - National Association of Community Health Centers
  - National Association of City & County Health Officials
  - American College of Preventive Medicine
  - National Association of Public Hospitals
  - American Pharmacists Association

The Safety Information Fact Sheet will be provided to MedWatch at the same time it is provided to these professional organizations.

The Safety Information Fact Sheet is appended and part of the REMS.

- d. In order to facilitate prescriber training and education, Gilead will disseminate printed safety information (above) about the use of TRUVADA for a PrEP indication to target healthcare providers through select professional scientific journals:
  - i. Journal information pieces will be published quarterly as printed information in the following professional society journals for 3 years following initial approval of the REMS:
    - Journal of the American Medical Association
    - Journal of the Academy of Family Physicians
    - Obstetricians and Gynecologists
    - Clinical Infectious Diseases
    - New England Journal of Medicine

The journal information pieces are appended and part of the REMS

- e. Gilead will ensure that, as part of training and education, the following materials are available to prescribers:
  - i.. **Dear Healthcare Provider (DHCP) letter** will include the potential and known risks associated with the use of TRUVADA for a PrEP indication and explain how to access the relevant training and education materials provided by Gilead. The letter will be sent to healthcare professionals who are likely to prescribe TRUVADA for a PrEP indication, as described in b. above. The letter will be sent within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 6, 12 and 24 months. The full Prescribing Information and Medication Guide will also be available with the DHCP letter. The letter will be available via a REMS-specific link from the TRUVADA REMS website ([www.truvadapreprems.com](http://www.truvadapreprems.com)) on the date of the first mailing.

Gilead will distribute the DHCP letter to the targeted prescribers via electronic mail, mail or facsimile.

- ii. **Important Safety Information about TRUVADA for a PrEP Indication for Healthcare Providers and Important Safety Information about TRUVADA for a PrEP Indication for Uninfected Individuals** will include both information directed to prescribers for education, as well as safety risk information for prescribers to use to educate uninfected individuals considering or taking TRUVADA for a PrEP indication.
- iii. Prescribers will have access to the **Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis (PrEP) of Sexually Acquired HIV-1 Infection** to be discussed with an uninfected individual taking TRUVADA for a PrEP indication. The Agreement Form will be for use at each visit to facilitate discussion of and promote understanding about the safety risks associated with use of TRUVADA for a PrEP indication, the importance of adherence to the recommended daily dosing regimen, monitoring HIV-1 test results, and screening for sexually transmitted infections. The prescriber and the uninfected individual will sign the Agreement Form and the form will be placed in the individual's medical record.
- iv. Prescribers will have access to a **Checklist for Prescribers** as a reminder for the management of an individual considering or taking TRUVADA for a PrEP indication, recommendations for screening laboratory tests results including a negative HIV-1 test result, sexually transmitted infections, signs and symptoms of acute HIV infection, vaccination, as needed, to ensure a comprehensive prevention strategy for prescribing TRUVADA for a PrEP indication in an uninfected individual.
- v. The posting on the REMS Website for TRUVADA for a PrEP Indication and/or a mailing will include the TRUVADA for a PrEP Indication Healthcare Professional Training and Education Program Kit which will consist of the following materials to support the training and educational process:
  - 1. Full Prescribing Information
  - 2. Medication Guide
  - 3. Dear Healthcare Provider Letter
  - 4. Training Guide for Healthcare Prescribers
  - 5. Prescriber Educational Slide Deck
  - 6. Important Safety Information about TRUVADA for a PrEP Indication for Healthcare Providers

7. Important Safety Information about TRUVADA for a PrEP Indication for Uninfected Individuals
8. Agreement Form For Initiating TRUVADA For Pre-Exposure Prophylaxis Of Sexually Acquired HIV-1 Infection for an uninfected individual taking TRUVADA for a PrEP Indication
9. Checklist for Prescribers to manage an individual considering or taking TRUVADA for a PrEP indication
10. Safety Information Fact Sheet

These materials are part of the REMS and are appended.

- f. Gilead will ensure that all materials listed in or appended to the TRUVADA for a PrEP Indication program will be available through the TRUVADA REMS program website, [www.truvadapreprems.com](http://www.truvadapreprems.com). This information will remain on the website for a period of 3 years from product approval.

### **C. Timetable for Submission of Assessments**

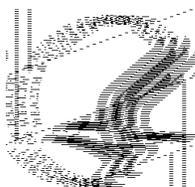
Gilead Sciences, Inc. will submit REMS Assessments to FDA at 6-months, 12-months, and annually, thereafter from the initial date of the approval (mm/dd/yy) of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Gilead Sciences, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

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/s/  
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KATHERINE SCHUMANN  
06/26/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-030

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets

**Date:** June 25, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-030 Truvada for a PrEP indication – Comments Regarding Proposed Labeling

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of June 21, 2012, containing revised labeling for TRUVADA.

The attached comments regarding the proposed TRUVADA prescribing information and Medication Guide are being communicated to you on behalf of the review team.

Please submit your response by Thursday, June 28, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

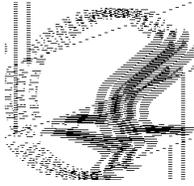
Enclosed: Draft Prescribing Information  
Draft Medication Guide

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/s/  
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KATHERINE SCHUMANN  
06/25/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** June 20, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Comments Regarding Prescriber Education Slide Deck

---

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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of June 4, 2012, containing revised REMS materials.

Please refer to the attached prescriber education slide deck containing comments and requested revisions from DAVP. In addition to incorporating the requested changes, please make any changes necessary to ensure that the slide deck is consistent with the current draft labeling for TRUVADA.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Enclosed: Prescriber education slide deck

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/s/  
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KATHERINE SCHUMANN  
06/20/2012

## Schumann, Katherine

---

**From:** Schumann, Katherine  
**Sent:** Monday, June 18, 2012 10:33 AM  
**To:** 'Dara Wambach'  
**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-30 Truvada - Information Request Regarding Observational Study and Revised PMR Proposal Document

**Attachments:** 2012\_06\_18 NDA 21752 S-30 Information Request.pdf; 2012\_06\_18 NDA 21752 S-30 PMR Drafts.doc

Dear Dara,

Please find attached the following two documents pertaining to NDA 21752 S-30:

1. Information request regarding your planned Observational Study, GS-US-164-0465.
2. PMR proposal document with DAVP's revisions.

Please let me know if you have any questions.

Warm Regards,

Katie



2012\_06\_18 NDA 21752 S-30 Info... 2012\_06\_18 NDA 21752 S-30 PMR ...

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993  
Tel: 301-796-1182  
Fax: 301-796-9883  
Email: Katherine.Schumann@fda.hhs.gov

Postmarketing Requirement Proposals

- 1) Collect data from individuals participating in demonstration projects who seroconvert during follow-up. The following data should be collected from a minimum of 150 seroconverters enrolled in demonstration projects:
- 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.
  - Frequency of screening and screening method(s) used for evaluation of the seroconverter, and in general, at that enrollment site.
  - Analyses of baseline samples for early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.
  - Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultra-deep sequencing of proviral DNA if no resistance is identified by population sequencing.

Timeline: Final protocol submission – (b) (4)  
 Periodic report submissions – Sept 2013, Sept 2014, Sept 2015  
 Final study report submission – Sept 2016

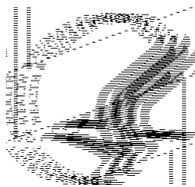
- 2) Prospectively follow 200 women who become pregnant while taking TRUVADA for pre-exposure prophylaxis and choose to continue these drugs during their pregnancies. Collect data on pregnancy outcomes that should include but not be limited to: HIV seroconversions in mother and infants, spontaneous and elective abortions, pre-term deliveries, stillbirths, infant weight (normal or low) and infant outcomes, including the presence or absence of congenital malformations. Data from a similarly sized comparator group should also be collected.

Timeline: Final protocol submission – (b) (4)  
 Study completion – (b) (4)  
 Final study report submission – (b) (4)

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/s/  
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KATHERINE SCHUMANN  
06/25/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** June 18, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Information Request

---

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/tenofovir disoproxil fumarate) tablets.

The following questions are being conveyed on behalf of DAVP and DRISK.

Please provide clarification about the REMS KAB surveys in the Observational Study Protocol, GS-US-164-0465:

1. Will the Knowledge, Attitude and Behavior (KAB) surveys for prescribers and uninfected individuals in the Gilead Observational Study Protocol be the same KAB surveys for prescriber and uninfected individuals in the REMS assessment?
2. If so, will the REMS appended educational materials be used in Gilead's Observational Study?
3. If the response is "yes", does Gilead plan to use all of the REMS appended educational materials or only some of the educational materials?

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

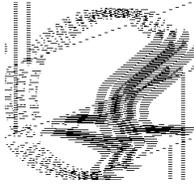
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
06/18/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-030

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets

**Date:** June 15, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-030 Truvada for a PrEP indication – Comments Regarding Proposed Labeling

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of June 8, 2012, containing revised labeling for TRUVADA.

The attached comments regarding the proposed TRUVADA prescribing information are being communicated to you on behalf of the review team.

Please submit your response by Wednesday, June 20, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Enclosed: Draft Prescribing Information

47 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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KATHERINE SCHUMANN  
06/15/2012

# MEMORANDUM OF TELECON

DATE: June 14, 2012

APPLICATION NUMBER: NDA 21752 S-030

BETWEEN

**Gilead Sciences, Inc:**

Andrew Cheng, MD, PhD, SVP, HIV Therapeutics & Development Operations  
Tobias Peschel, MD, PhD, VP, Drug Safety and Public Health  
James F. Rooney, MD, VP, Medical Affairs  
Michael Wulfsohn, MD, PhD, VP Biometrics  
Michael Miller, Ph.D., Senior Director, Clinical Virology  
David Pizzuti, MD, VP, Regulatory Affairs  
Paul Tomkins, PhD, Senior Director, Regulatory Affairs  
Dara Wambach, MA, Associate Director, Regulatory Affairs

AND

**DAVP:**

Debra Birnkrant, Director, DAVP  
Jeffrey Murray, Deputy Director, DAVP  
Kendall Marcus, Safety Deputy Director, DAVP  
Peter Miele, Medical Officer, DAVP  
Damon Deming, Clinical Virology Reviewer, DAVP  
Eric Donaldson, Clinical Virology Reviewer, DAVP  
Jules O'Rear, Clinical Virology Team Leader, DAVP  
Ruben Ayala, Clinical Pharmacology Reviewer, DCP4, OCP  
Kyong Hyon, Safety Project Manager, DAVP  
Victoria Tyson, Chief, Project Management Staff, DAVP  
Katherine Schumann, Regulatory Project Manager, DAVP  
Carolyn Yancey, DRISK, OSE  
Anahita Tavakoli, DRISK, OSE  
Claudia Manzo, DRISK, OSE  
Judy Staffa, DEPI II, OSE  
James Trinidad, DEPI II, OSE  
Grace Chai, DEPI II, OSE

**SUBJECT:** FDA's proposed PMRs and PMC for NDA 21752 S-030

**BACKGROUND:** On December 14, 2011, Gilead submitted an efficacy supplement (NDA 21752 S-030) for a new indication for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) for pre-exposure prophylaxis of HIV-1.

A teleconference was held between the FDA and Gilead on June 14, 2012, to discuss the Division's two proposed PMRs and one proposed PMC for this efficacy supplement. Please refer to the attached PMR and PMC proposals, sent to the applicant via email on June 13, 2012.

## **DISCUSSION POINTS:**

### **PMR #1**

**Collect data from individuals participating in demonstration projects who seroconvert during follow-up. The following data should be collected from a minimum of 150 seroconverters enrolled in demonstration projects:**

- 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. Analyses of baseline samples for early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.**
- c. Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultra-deep sequencing of proviral DNA if no resistance is identified by population sequencing.**

**Timeline:**      **Final protocol submission – (b) (4)**  
**Periodic report submissions –Sept 2013, Sept 2014, Sept 2015**  
**Final study report submission – Sept 2016**

Gilead explained that it is feasible for them to collect information on 150 seroconverters from the ongoing and planned demonstration projects being conducted by other organizations. However, before committing to provide the full resistance analyses requested by the Agency for all 150 participants, they will need to speak to the organizations sponsoring the studies. Gilead agreed to provide an update in the next week to 10 days. The Division reminded Gilead to provide a specific number of subjects from whom they can collect the requested data, so that the PMR can be worded as concretely as possible.

Gilead asked the Division if it is necessary to perform ultra-deep sequencing of proviral DNA or if another technique might be acceptable, such as sequencing plasma RNA. The Division replied that alternative techniques can be submitted for review. The Division also requested that Gilead submit information on the performance of their sequencing methods, once a protocol is prepared.

The Division also explained that the rationale for requesting data from 150 seroconverters is aimed at powering the study to show that the rate of resistance seen with post-marketing use is not very different than what was seen in the submitted clinical trials. If the rate seen in the demonstration projects exceeds the upper bound of the range from the trials, the Division would consider it a signal requiring further evaluation.

### **PMR #2**

**Prospectively follow 200 women who become pregnant while taking TRUVADA for pre-exposure prophylaxis and choose to continue these drugs during their pregnancies. Collect data on pregnancy outcomes that should include but not be limited to: HIV seroconversions in mother**

and infants, spontaneous and elective abortions, pre-term deliveries and infant outcomes, including the presence or absence of congenital malformations.

Timeline: Final protocol submission – (b) (4)  
Study completion – (b) (4)  
Final study report submission – (b) (4)

Gilead asked if it would be acceptable for them to (b) (4)

(b) (4)

(b) (4)

Gilead agreed to follow up regarding both possible options for collecting this data and come back to the Division with a proposal for the PMR.

#### PMC

Provide nationally representative drug utilization data to FDA of sufficient detail that use of Truvada for a PrEP indication and individuals using Truvada for a PrEP indication can both be characterized. This data should be submitted to FDA every 6 months for three years, for both generic and brand name products containing FTC/TDF, starting at one year following approval of 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 demonstration projects performed in the United States in terms of patient demographics, patient clinical characteristics, prescriber specialties, settings of care, and geographic region (when available).

**Timeline for submission:**

- 1) Final protocol – (b) (4)
- 2) Interim reports – July 2013, January 2014, July 2014, January 2015, July 2015, January 2016
- 3) Final study report – July 2016

(b) (4)

(b) (4) the Agency would like Gilead to propose a strategy using multiple sources that would represent different settings of care in the United States.

Gilead asked for clarification regarding the request for data for generic products, given that both tenofovir DF and emtricitabine are still under patent. Grace Chai replied that the purpose of the request is to obtain data on use of the individual components (tenofovir DF and emtricitabine) for the PrEP indication, as well as the fixed-dose combination TRUVADA. Gilead agreed that this could be done.

**Demonstration Project (Observational Study Protocol GS-US-164-0465)**

The Division explained that it is still considering the option of making Gilead's planned demonstration project into a PMC, but is not yet prepared to discuss the details. Specifically, the Division would like a more thorough evaluation of adherence in as broad of a geographic range as possible. Strategies for obtaining this information might include questionnaires to associate risk factors with outcomes, as well as objective measures of adherence such as drug levels from plasma or hair samples.

Gilead replied that their demonstration project is a registry and is not designed to collect laboratory data of any kind. However, Gilead agreed to explore the possibility of collecting this information as part of another demonstration project.

**Labeling**

The Division requested that Gilead revise three sections of the draft labeling.

- 1) Language concerning renal impairment

The Division expressed concern that patients who start out with normal renal function will not be discontinued from PrEP until CrCl is below 50 mL/min. The Division asked the company to propose language for more conservative management of patients, perhaps recommending discontinuation of PrEP after a certain percentage change in CrCl.

- 2) Testing for acute infection

The Division explained that they were still of the opinion that the PI should recommend a test sensitive to acute infection (not just a "highly sensitive diagnostic")

prior to initiation of PrEP to prevent individuals from starting PrEP with undiagnosed acute infection and possibly develop resistance. Gilead agreed to re-consider that request and propose alternative language for testing.

3) Language concerning drug level substudies in Section 14

The Division asked Gilead to remove specific values of risk reduction derived from the post-hoc case control studies for both iPrEx and Partners PrEP and replace the language with qualitative statements regarding the correlation between drug levels/adherence and efficacy. Gilead agreed to revise the wording, but expressed concern that prescribers might ask the company for further information on how that correlation was established. The Division agreed to consult with OPDP regarding this concern.

**ACTION ITEMS:**

1. Gilead will update the Division in one week to 10 days with specific proposals to address the two PMRs and one PMC, including the number of subjects from whom they will obtain the requested resistance data.
2. DAVP will provide written labeling comments to Gilead, including the three issues discussed during the meeting.

Attachments:

PMR Proposal Document dated June 13, 2012

PMC Proposal Document dated June 13, 2012

Postmarketing Requirement Proposals

- 1) Collect data from individuals participating in demonstration projects who seroconvert during follow-up. The following data should be collected from a minimum of 150 seroconverters enrolled in demonstration projects:
  - 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. Analyses of baseline samples for early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.
  - c. Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultra-deep sequencing of proviral DNA if no resistance is identified by population sequencing.

Timeline: Final protocol submission – (b) (4)  
Periodic report submissions – Sept 2013, Sept 2014, Sept 2015  
Final study report submission – Sept 2016

- 2) Prospectively follow 200 women who become pregnant while taking TRUVADA for pre-exposure prophylaxis and choose to continue these drugs during their pregnancies. Collect data on pregnancy outcomes that should include but not be limited to: HIV seroconversions in mother and infants, spontaneous and elective abortions, pre-term deliveries and infant outcomes, including the presence or absence of congenital malformations.

Timeline: Final protocol submission – (b) (4)  
Study completion – Sept 2014  
Final study report submission – March 2015

## Truvada for a PrEP Indication Post-marketing Commitment

Provide nationally representative drug utilization data to FDA of sufficient detail that use of Truvada for a PrEP indication and individuals using Truvada for a PrEP indication can both be characterized. This data should be submitted to FDA every 6 months for three years, for both generic and brand name products containing FTC/TDF, starting at one year following approval of 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
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    - i. Unique incident users every quarter-year
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  - 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 demonstration projects performed in the United States in terms of patient demographics, patient clinical characteristics, prescriber specialties, settings of care, and geographic region (when available).

Timeline for submission:

- 1) Final protocol – (b) (4)
- 2) Interim reports – July 2013, January 2014, July 2014, January 2015, July 2015, January 2016
- 3) Final study report – July 2016

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/s/  
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KATHERINE SCHUMANN  
07/15/2012



NDA 21752/S-030

**REVIEW EXTENSION –  
EFFICACY SUPPLEMENT**

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 December 14, 2011 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRUVADA<sup>®</sup> (emtricitabine 200 mg /tenofovir disoproxil fumarate 300 mg).

On June 5, 2012, we received your June 4, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 14, 2012.

If you have questions, call Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

Sincerely,

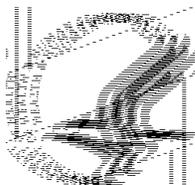
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Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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DEBRA B BIRNKRANT  
06/05/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** June 4, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Revised REMS document

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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/tenofovir disoproxil fumarate) tablets.

Please find attached the Agency's REMS Document with additional revisions made to the version you submitted on May 8, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

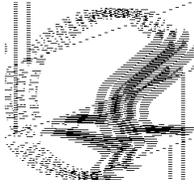
Attachment: REMS document

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/s/  
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KATHERINE SCHUMANN  
06/04/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-030

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets

**Date:** June 1, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-030 Truvada for a PrEP indication – Comments Regarding Proposed Labeling

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of May 21, 2012, received May 22, 2012, containing revised labeling for TRUVADA.

The attached comments regarding the proposed TRUVADA prescribing information are being communicated to you on behalf of the review team.

Please submit your response by Thursday, June 7, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

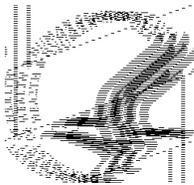
Enclosed: Draft Prescribing Information

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KATHERINE SCHUMANN  
06/01/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** May 30, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Additional REMS Comments

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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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of May 8, 2012, containing amendments to the REMS proposal.

The following are required revisions to the REMS proposed for Truvada for a PrEP Indication that must be completed for the REMS to be acceptable to the Agency. The Agency requests that responses to these comments be submitted to the Agency by close of business on June 4, 2012. If this is not possible, notify the Agency as soon as possible as to the expected submission date of these revised and new materials. Please note that additional revisions to the REMS document are forthcoming, and it is not necessary for you to revise the REMS document at this time.

**Required Terminology Revisions**

Persons considering or taking Truvada for a PrEP indication are not considered (b) (4) being “treated” rather they are considered “uninfected individuals” “taking” Truvada for a PrEP indication. Based on this rationale, the Agency requires that “treated/treatment” be replaced with “taking/having taken” throughout the REMS, all appended materials and the REMS Supporting Document.

**Comments on Proposed REMS**

## 1. REMS ELEMENTS

### a. Medication Guide (applicable to all approved indications)

The Medication Guide will remain as an element in the REMS proposed for Truvada for a PrEP indication. Comments about the Medication Guide will be forthcoming under separate communication

### b. Element to Assure Safe Use (ETASU): Prescriber Training and Education

Based on feedback from the Antiviral Drugs Advisory Committee, Prescriber Training and Educational materials must be strengthened to more actively convey important safety risk information with use of TRUVADA for a PrEP indication. Revise the ETASU prescriber training and education materials as follows:

i. Delete [REDACTED] (b) (4)

ii. Delete the [REDACTED] (b) (4)

Develop and submit the following new training and educational materials:

iii. Journal Information Pieces: To facilitate prescriber training and education, you must develop and disseminate printed information about the safe and appropriate use of Truvada for PrEP as well as the known and potential safety risks associated with use of TRUVADA for a PrEP indication to professional scientific journals. Consider journals that reach primary care physicians and other professional journals targeted to healthcare providers that are likely to prescribe Truvada for PrEP. Journal information pieces will be published quarterly as printed information for 3 years following product approval.

*As an example, see the ACTEMRA REMS website with journal information pieces.*

iv. Prescriber Education Slide Deck: For face-to-face presentations by Gilead Medical Science Liaisons with prescribers in an office practice, community clinic, hospital grand rounds, or larger professional meeting. Consider the Full Prescribing Information as supportive information to the prescriber educational slide deck.

v. Safety Information Fact Sheet: For dissemination to key professional organizations as outreach to likely target healthcare providers of TRUVADA for a PrEP indication (see proposed REMS, Section II. B. 1. c.). Propose and submit the names of key professional organizations that will disseminate a Safety Information Fact Sheet to likely prescribers of Truvada for a PrEP indication

vi. Prescriber-Individual Agreement Form To be reviewed by a prescriber with an individual considering or taking TRUVADA for a PrEP indication. This Agreement Form must include key safety risk information, recommended HIV-1 testing prior to and regularly throughout taking TRUVADA for a PrEP indication, and the importance of adherence with a comprehensive program including practicing safer sex. This form is intended to be signed by the prescriber and individual for placement in the individual's medical record.

- vii. Checklist for Prescribers: To serve as reminder of key safety risk messages, the importance of counseling an individual about the need for regular HIV-1 monitoring and adherence with taking a daily dose of Truvada for a PrEP indication. A Checklist must include, for example, the following:
- a) Discussion of known safety risks with use of TRUVADA for a PrEP indication with an individual considering or taking TRUVADA for a PrEP indication
  - b) Importance of HIV-1 testing immediately before first prescribing Truvada for a PrEP indication and regularly monitoring an individual taking Truvada for a PrEP indication every 2 to 3 months before giving them another prescribing for Truvada for a PrEP indication
  - c) Importance of adherence with taking a daily dose of TRUVADA to lower the risk for getting HIV-1 infection
  - d) Importance of regular monitoring of HIV-1 serostatus to avoid continuing to take TRUVADA for a PrEP indication, if seroconversion has occurred, to reduce the development of resistant HIV-1 variants
  - e) Importance of taking TRUVADA for a PrEP indication as part of a comprehensive prevention strategy
  - f) Practicing safer sex consistently and correctly to reduce the risk of HIV-1 infection
  - g) Knowing their HIV-1 status and that of their partner(s), if possible
  - h) Screening for sexually transmitted infections (STIs) that can facilitate HIV-1 transmission (such as syphilis and gonorrhea)
- c. Timetable for Submission of Assessments: as amended is acceptable.

### **Comments on REMS Appended Materials**

1. Dear Healthcare Provider letter: see the track changes in the **Attachment**.
2. Important Safety information about TRUVADA for a PrEP indication in Uninfected Individuals: See track changes in the **Attachment**.

Page 6: **When you should not take TRUVADA for a PrEP indication**, 2<sup>nd</sup> bullet:

(b) (4)  
Delete comment and make consistent with final pregnancy labeling.

Page 7: **Things to tell your healthcare provider**, 2<sup>nd</sup> bullet: Delete second sentence

(b) (4)  
Make consistent with final labeling.

Page 9: Common side effects of TRUVADA: Delete the first section “(b) (4) this claim minimizes the risks associated with Truvada use because there is no evidence in the label to support this claim.

3. Important Safety information about TRUVADA for a PrEP indication for Healthcare Providers: See track changes in the **Attachment**.

**Page 2: About TRUVADA for a PrEP indication to reduce the risk of HIV acquisition**

The presentation of the indication is inadequately communicated in the 1<sup>st</sup> paragraph: “ (b) (4)

Revise sentence as follows: “TRUVADA is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults”

**Page 3: WARNINGS:** (b) (4)

Revise this sentence to be consistent with label as follows: “Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue TRUVADA.”

**Page 4: TRUVADA for a PrEP indication: Warnings and Precautions** Add “at high risk” to all uninfected individuals to read as “uninfected individuals at high risk”

**Page 5: Use of TRUVADA for a PrEP indication in specific populations 1<sup>st</sup> bullet:** (b) (4)

.” Delete comment and make consistent with final pregnancy labeling.

4. TRUVADA for a PrEP Indication Training Guide for Healthcare Providers  
(See track changes in the **Attachment**)

**Page 1: About TRUVADA for a PrEP indication to reduce the risk of HIV acquisition**

The presentation of the indication is inadequately communicated in the 1<sup>st</sup> paragraph: (b) (4)

. Revise sentence as follows: “TRUVADA is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults”

**Page 3: WARNINGS: 2<sup>nd</sup> Bullet:** (b) (4)

” Revise this sentence to be consistent with label as follows: “Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue TRUVADA.”

**Page 6: Use of TRUVADA for a PrEP indication in specific populations 1<sup>st</sup> bullet:** (b) (4)

Delete comment and make consistent with final pregnancy labeling.

**Page 7: Confirm and regularly reconfirm negative HIV status 2<sup>nd</sup> bullet:**

Revise statement as follows: Individuals should be regularly tested **while taking** TRUVADA for a PrEP indication to reconfirm that they are HIV negative

**Page 10:** Review questions - Add a question about whether or not the prescriber explained the Prescriber-Individual Agreement form and if the individual as asked to sign the Agreement Form with the prescriber. Add a question about the Checklist for

Prescribers. Ask if this document was discussed as a guide for monitoring an individual's adherence to taking TRUVADA for a PrEP indication.

Back cover: Remove (b) (4) from list of educational materials to order; Change "Tagline" from (b) (4)

(b) (4) to "Help uninfected individuals learn more about TRUVADA for a pre-exposure prophylaxis (PrEP) indication"

5. (b) (4) Delete TRUVADA (b) (4)
6. REMS website landing page ([www.truvadapreprems.com](http://www.truvadapreprems.com))
  - a. Revise the 1<sup>st</sup> page (REMS landing page) on the [truvadapreprems.com](http://truvadapreprems.com) website to clearly state the following language as background information:
    - i. A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.
    - ii. To make sure Truvada for a PrEP indication is prescribed and taken safely, Gilead has worked with the FDA to develop materials for the REMS program to educate and inform healthcare professionals and uninfected individuals at high risk for acquiring HIV-1.
  - b. Remove the goals of the REMS from the REMS website page.
  - c. You repeated the same Important Safety Information on TRUVADA on each screen of the website. Only place the Important Safety Information About TRUVADA on the first page, not on subsequent pages. You may elect to use a link to Important Safety Information for TRUVADA on subsequent screens if you choose.

### **REMS Assessment Plan**

1. An analysis of the safety profile of Truvada for a PrEP indication when taken as part of a comprehensive program to reduce the risk of acquiring HIV-1 and information received from adverse event reporting is too broad to include in assessment of whether the REMS is meeting its goals.
2. The assessment plan should include, to the extent that you are able to ascertain this information:
  - a. Reports of drug resistance in individuals who seroconvert during use of TRUVADA as monotherapy
  - b. Compliance with HIV testing in individuals using TRUVADA for a PrEP indication
3. Knowledge, Attitude and Behavior Surveys for Prescribers/Uninfected Individuals
  - a. You state that due to inherent delay in availability of data regarding awareness and use of Truvada for a PrEP indication, that the initial KAB survey results will not be available for the 6-month assessment report.

Action Step:

Clarify why you conclude that preliminary data will not be available by the 6-month REMS assessment and propose a timeline within which you propose to submit KAB survey results to the Agency.

- b. Include questions about the Prescriber-Individual Agreement Form
- c. Include questions about the Checklist for Prescribers

**REMS Supporting Document**

The REMS Supporting Document must be consistent with all revisions to the REMS Document and all appended REMS materials including the REMS website.

**Resubmission instructions:**

Submit the amendments to the REMS proposed for Truvada for a PrEP indication with all appended REMS materials, the REMS website landing page and subsequent screen shots, and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all (each) revised material and document. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other appended REMS materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. However, to work efficiently in each document, we request a separate WORD document for each appended material. If certain documents are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

---

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Attachments: Dear Healthcare Provider Letter  
Important Safety Information for Uninfected Individuals  
Important Safety Information for Healthcare Providers  
Training Guide for Healthcare Providers

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

# MEMORANDUM OF TELECON

DATE: May 17, 2012

APPLICATION NUMBER: NDA 21752 S-030

BETWEEN

**Gilead:**

Andrew Cheng, MD, PhD, SVP, HIV Therapeutics & Development Operations  
Tobias Peschel, MD, PhD, VP, Drug Safety and Public Health  
James F. Rooney, MD, VP, Medical Affairs  
Keith Rawlings, MD, Director, Medical Affairs  
David Pizzuti, MD, VP, Regulatory Affairs  
Paul Tomkins, PhD, Senior Director, Regulatory Affairs  
Dara Wambach, MA, Associate Director, Regulatory Affairs

AND

**DAVP:**

Debra Birnkant, MD, Director, Division of Antiviral Drug Products (DAVP)  
Kendall Marcus, MD, Deputy Director for Safety, DAVP  
Peter Miele, MD, Medical Officer, DAVP  
Carolyn Yancey, MD, Medical Officer, DRISK  
Kendra Worthy, PharmD, Team Leader, DRISK  
Shirley Seo, PhD, Acting Team Leader, Clinical Pharmacology, DCP 4  
Ruben Ayala, PhD, Clinical Pharmacology Reviewer, DCP 4  
Leyla Sahin, MD, Medical Officer, Pediatric and Maternal Health Staff  
Victoria Tyson, Chief, Project Management Staff, DAVP  
Kyong Hyon, RN, MA, Safety Regulatory Project Manager, DAVP  
Katherine Schumann, MS, Regulatory Project Manager, DAVP

**SUBJECT:** Post-Advisory Committee meeting update regarding Truvada supplement S-30

**BACKGROUND:** On December 14, 2011, Gilead submitted an efficacy supplement (NDA 21752 S-030) for a new indication for Truvada (emtricitabine/tenofovir disoproxil fumarate) for pre-exposure prophylaxis of HIV-1.

At the Advisory Committee meeting held on May 10, 2012 to discuss the supplement, the committee members provided a number of recommendations regarding the labeling and REMS for Truvada for a PrEP indication. DAVP held a debriefing with CDER Director Janet Woodcock on May 16, 2012, to determine how to incorporate feedback from the advisory

committee into the Division's review of the supplement. Based upon the discussion with Dr. Woodcock, DAVP decided to request a number of changes to the labeling and REMS.

A teleconference was held between the Division and Gilead on May 17, 2012, to communicate requested revisions to the labeling and REMS.

### **DISCUSSION POINTS:**

The Division and Gilead discussed the following items:

#### **With regards to the label:**

1. Addition of "**must rule out HIV infection prior to initiation of Truvada for a PrEP indication**" in the box warning.

*Discussion: Gilead agreed.*

2. Addition of **contraindication** to use of Truvada for a PrEP indication in HIV-infected persons.

*Discussion: Gilead expressed reluctance to add this contraindication in addition to the new box warning language. The Division explained that it would be important to have strong labeling in lieu of a REMS with ETASU tied to restricted distribution, given the feedback from the Advisory Committee. Gilead proposed submitting two revised drafts of the labeling, one with the contraindication and one without, for the Division to review. The Division agreed to this proposal.*

3. Addition of language about recommended - "highly sensitive diagnostic" - test(s) for determining HIV status at baseline and during PrEP follow-up.

*Discussion: Gilead asked the Division for additional details about the type of tests that would be considered "highly sensitive." The Division agreed to consult with its clinical virology team and then provide feedback to Gilead.*

4. Addition of the phrase "**adults at high risk**" to indication.

*Discussion: Gilead agreed, but raised the point concern that "high risk" may be difficult to define, other than using the enrollment criteria from iPrEx and Partners PrEP.*

5. Addition that PrEP should not be initiated in individuals with creatinine clearance less than 60 mL/min and that PrEP should be stopped in individuals with creatinine clearance <50 mL/min.

*Discussion: Gilead agreed.*

6. Addition of recommendation to do more sensitive testing to rule out HIV infection in individuals with signs or symptoms of acute infection.

*Discussion: Gilead agreed.*

7. Addition of a description of signs and symptoms of acute infection to the label with reference:

Daar ES, Pilcher CD, Hecht FM. Clinical presentation and diagnosis of primary HIV-1 infection. *Curr Opin HIV AIDS*. Jan 2008;3(1):10-15.

Vanhems P, Routy JP, Hirschel B, et al. Clinical features of acute retroviral syndrome differ by route of infection but not by gender and age. *J Acquir Immune Defic Syndr*. Nov 1 2002;31(3):318-321.

*Discussion: Gilead agreed.*

8. Revision of pregnancy section to remove recommendation (b) (4) to reflect risk-benefit assessment of taking PrEP during pregnancy. This may include, but does not need to be limited to, seroconversions in Partners PrEP while on treatment interruption for pregnancy and increased risk for HIV acquisition during pregnancy:

Gray RH, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet*. Oct 1 2005;366(9492):1182-1188.

*Discussion: Gilead asked the Division for more specific detail on the information that would be appropriate to include in this section. The Division agreed to get back to Gilead with a more specific request after further consultation with Maternal Health staff.*

9. Addition of clinical trial experience in uninfected individuals taking Truvada for PrEP and bone mineral density loss (Section 5.5).

*Discussion: Gilead agreed.*

#### **Advertising:**

10. We would like to gain agreement on submission of all PrEP advertising to FDA prior to implementation.

*Discussion: Gilead explained that they (b) (4)*

**REMS:**

11. Delete [REDACTED] (b) (4) from target prescribers for training and education.

*Discussion: Gilead agreed.*

12. Delete [REDACTED] (b) (4) from prescriber training and education materials

*Discussion: Gilead agreed.*

13. Develop/submit **Journal Information Pieces** to be placed in key professional journals of the target prescribers. Journal information pieces only include known safety risk information directed to prescribers/healthcare professionals.

*Discussion: Gilead asked for additional information to clarify the nature of a Journal information piece. Specifically, Gilead asked if the piece would be similar to a journal advertisement. DRISK replied that it is not an advertisement, and only includes safety risk information. DRISK agreed to share examples of published information pieces with Gilead.*

*Gilead also asked if the prescribers targeted with the Journal information piece had to be the same as those targeted with the safety information fact sheet through professional organizations. DRISK replied that Gilead should propose the journals to which they plan to send the information piece, but that they did not need to target the same prescribers.*

14. Develop/submit a **prescriber education slide deck** to inform target prescribers about the known safety risks with use of TRUVADA for a proposed PrEP indication. The prescriber educational slide deck must be developed with the intent of face-to-face presentation by "experts" and/or Medical Science Liaisons per the applicant. Consider the Full Prescribing Information as supportive to a focused prescriber educational slide deck.

*Discussion: Gilead asked if they could use [REDACTED] (b) (4) and Medical Science Liaisons. DRISK agreed in principle, but said that a final decision would be dependent upon review of the slides submitted by the company.*

15. Develop/submit a single-page, **Safety Information Fact Sheet** for dissemination to key professional organizations (2 to 3) with outreach to likely target prescribers of TRUVADA for a PrEP indication

*Discussion: Gilead agreed, but asked for an example. DRISK replied that an example had already been sent. Gilead confirmed they had received it.*

16. Develop/submit a **Prescriber-Individual Agreement Form** to be reviewed with an individual (considering / taking TRUVADA for a PrEP indication). Include key risk

messages, HIV-1 testing and regular monitoring, the importance of adherence with a comprehensive program including practicing safer sex. The Agreement Form must include space for signatures of the prescriber and individual. This document will be placed in the individual's medical record.

*Discussion: Gilead agreed.*

17. Develop/submit a **Checklist for Prescribers** to be placed in the individual's medical record.

*Discussion: Gilead asked whether the FDA or the company would be responsible for monitoring physician use of the prescriber-individual agreement form and the checklist for prescribers. DRISK replied that it would be voluntary for physicians to use these tools, but that Gilead would be asked to evaluate their use as part of the REMS assessment (for example, as a question in the KAB surveys). Gilead agreed.*

Following these items, Gilead explained they were working with the Partners PrEP study team and laboratory to address the Division's request for the Partners PrEP bioanalytical report, but did not yet have an estimated date for submission.

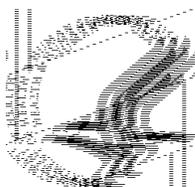
#### **ACTION ITEMS:**

1. Gilead will prepare and submit revised labeling as soon as possible. [Post-meeting note: The revised labeling was submitted and received on 5/21/12.]
2. DAVP will provide feedback regarding the HIV diagnostic tests to be recommended in the labeling for Truvada for a PrEP indication.
3. DRISK will provide examples of journal information pieces to Gilead.
4. Gilead will address the requested changes to the REMS, including the new prescriber education and training materials.
5. Gilead will update the Division on the timeline for submission of the Partners PrEP bioanalytical report.

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KATHERINE SCHUMANN  
07/15/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-030

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate) tablets

**Date:** May 17, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-030 Truvada for a PrEP indication – Comments Regarding Proposed Labeling

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. The following comments regarding the PI are being communicated on behalf of the review team. Please note that these are preliminary comments, and further revisions will be communicated at a later date, including revisions to the Prescribing Highlights and Medication Guide.

1. In addition to the comments already conveyed to you about revision of the Pregnancy section, we request that summary data on infant outcomes following exposure to emtricitabine and tenofovir during pregnancy as reported to the Antiretroviral Pregnancy Registry be added. You may refer to the current Reyataz® package insert for content and format.
2. Add "in combination with safer sex practices" to the indication.
3. BOX warning should include requirement for a negative HIV-1 test result prior to and during treatment with TRUVADA for a PrEP indication.

Please also refer to the items discussed during the teleconference of May 17, 2012, as well as the attached PI, for specific comments.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Enclosed: Draft Prescribing Information

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KATHERINE SCHUMANN  
05/17/2012

## MEMORANDUM OF TELECON

DATE: May 16, 2012

APPLICATION NUMBER: NDA 21752 S-030

BETWEEN:

Name: Dara Wambach, M.A.  
Associate Director, Regulatory Affairs  
Gilead Sciences, Inc.  
Phone: (650) 522-5163

AND

Name: Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products

SUBJECT: Submission of a bioanalytical report for Partners PrEP trial drug level data

On May 16, 2012, at the request of Ruben Ayala, Ph.D., and Shirley Seo, Ph.D., I spoke to Dara Wambach of Gilead Sciences to request submission of a bioanalytical report for the Partners PrEP trial submitted in NDA 21752 Supplement 30.

I noted that, in Gilead's correspondence of March 8, 2012, responding to the Division's request of January 20, 2012, Gilead provided a method validation report and standard operating procedure for the quantitation of emtricitabine and tenofovir in human plasma. I mentioned that they had not responded to the full request, however, as they had not submitted key information typically contained in a bioanalytical report: information describing how the procedures (sample handling, analysis, generation of data) were carried out in the context of the trial. I informed Ms. Wambach that this information was necessary to support wording regarding plasma levels of drug from the Partners PrEP trial proposed by Gilead for inclusion in the labeling.

Ms. Wambach committed to take this request to the Partners PrEP study team and corresponding bioanalytical laboratory. She will respond with the feasibility and timing of providing the missing information to the supplemental NDA for review.

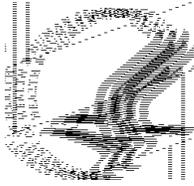
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 30, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Clinical Information Request

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following is a request for clinical information from Study CDC 4323.

For Subject S197, in the immediate TDF cohort, please provide clinical information regarding the adverse event of vertebral fracture, reported on four separate dates.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

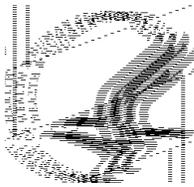
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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KATHERINE SCHUMANN  
04/30/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 26, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Through:** Damon Deming, Ph.D., Clinical Virology Reviewer  
Jules O'Rear, Ph.D., Clinical Virology Team Leader  
Kendall Marcus, M.D., Cross-Disciplinary Team Leader

**Subject:** NDA 21752 S-30 Truvada PrEP – Clinical Virology Comments

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

Please also refer to your April 24, 2012 response to the Agency's information request of April 13, 2012 and to your draft presentations for the May 10, 2012 Advisory Committee meeting, submitted on April 24, 2012.

The following comments are being conveyed to you on behalf of the review team.

1. Please provide a detailed discussion about the original misidentification of K65N in Subject 5241418 of the Partner's PrEP trial, including additional information on the collection dates of the samples (if different), the relative sensitivities of the assays to minority variants (if different), or other methodological changes that might have affected assay sensitivity.
2. Please indicate if the frequencies of the individual HIV-1 subtypes that were observed among subjects of the Partner's PrEP study (for both partner and index subjects, if available) were representative of those prevalent in the areas of the study sites and comment on the relative efficacies of chemoprophylaxis against the different clades.

3.

(b) (4)



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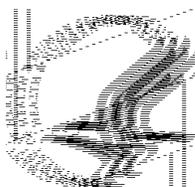
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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04/26/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 26, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – REMS Comments

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following comments and responses are from the Office of Surveillance and Epidemiology, the Division of Risk Management, to Gilead Sciences, Inc., regarding questions to the Agency dated April 18, 2012 and April 22, 2012. These responses and requirements supersede previous comments from the Agency.

REMS Document

1. Revise the REMS website name to be [www.truvadapreprems.com](http://www.truvadapreprems.com) in the following sections of the proposed REMS Document:
  - a. Section II., B. 1., a.
  - b. Section II., B., 1., d., i.
  - c. Section II., B., 1., d., iv.
  - d. Section II., B., 1., e.

REMS website

1. The Agency requires that the REMS website, [www.truvadapreprems.com](http://www.truvadapreprems.com), be independent of links to the promotional and/or commercial website as well as non-REMS materials about the product. Do not include a link from the REMS

website page

(b) (4)

however, if you choose, non-REMS materials and services can be located on and/or linked to the product website, [www.truvadaprep.com](http://www.truvadaprep.com).

2. The Truvada PrEP REMS webpage is required to be accessible directly through a search engine.

### REMS Assessments

1. You may maintain a database of prescribers who completed the training and education program (online or via hard copy). You may elect to use the prescriber database to link prescribers to non-REMS support materials and services such as vouchers for free HIV testing, condoms, subsidized testing for persons who converted from HIV-1 negative to HIV-1 positive, an opt-in reminder service, and/or support for community educational materials.
2. The REMS Assessment must report on the following:
  - a. Number and type of prescribers (by specialty) who completed the training and education program via the Gilead REMS website or through mailings. These data will be reported in the 6-month assessment
  - b. Results from the self-administered Knowledge, Attitude and Behavior survey of prescribers who prescribed TRUVADA for a PrEP indication about the key risk messages, including the importance of strict adherence to the dosing regimen, regular HIV-1 testing and adherence to the comprehensive prevention strategy to assess the effectiveness of the REMS education program
  - c. Results from the self-administered Knowledge, Attitude and Behavior survey of uninfected individuals taking TRUVADA for a PrEP indication about the key risk messages, including the importance of strict adherence to the dosing regimen, regular HIV-1 testing and adherence to a comprehensive prevention strategy to assess the effectiveness of the REMS education program
  - d. Number and type of prescriber (by specialty) who prescribed TRUVADA for a PrEP indication
  - e. Drug-use data, specifically, the number of TRUVADA prescriptions written for a PrEP indication; these data will be reported in the 6-month assessment

### Timetable for Submission of REMS Assessments

*Use the following text:*

Gilead Sciences, Inc. will submit REMS Assessments to FDA at 6-months, 12-months, and annually, thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for

that assessment. Gilead Sciences, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

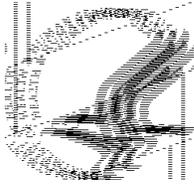
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 18, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Revised REMS document

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

Please find attached the Agency's REMS Document with additional revisions made to the version sent to you on March 30, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

Attachment: REMS document

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**D. Timetable for Submission of Assessments**

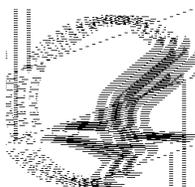
Gilead Sciences, Inc. will submit REMS assessment to FDA at 6 months, 18 months, 3 years, and 7 years from the initial date of the approval (mmddyy) of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Gilead Sciences, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

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/s/  
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KATHERINE SCHUMANN  
04/18/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 13, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Through:** Damon Deming, Ph.D., Clinical Virology Reviewer  
Jules O'Rear, Ph.D., Clinical Virology Team Leader  
Kendall Marcus, M.D., Cross-Disciplinary Team Leader

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Clinical Virology Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following requests are being conveyed to you on behalf of the review team.

1. Please verify that the RT-PCR assays that were used to detect and quantify plasma HIV-1 RNA (i.e., the Abbott RealTime HIV-1 or the Roche Amplicor HIV-1 Monitor tests for the iPrEx trial and the Abbott RealTime HIV-1 for Partner's PrEP) were also used to detect HIV-1 RNA in baseline samples of early seroconverters. If these assays were not used, please identify the assay(s) and provide a detailed description of its methodology and performance parameters if that information has not been submitted.
2. Please identify the HIV-1 strain used as the reverse transcriptase amino acid reference for the genotypic data from the iPrEx trial as presented in the "DERRESI" dataset.
3. We note that the resistance changes reflected in Amendment 1 of the Clinical Study Report of CO-US-104-0380, dated 20 February 2012, were not included in the preliminary manuscript submitted on 21 March 2012. Please verify that the authors intend to remove the

identification of <sup>(b) (4)</sup> as a TDF resistance-associated substitution from the manuscript prior to submission for publication.

4. There were long delays between the detection of seroconversion by rapid anti-HIV-1 antibody tests and the detection of viral RNA in some subjects of Study CO-US-104-0380 (i.e., Subjects 5044313 and 5657618 had 420 and 254 days, respectively, between the time of seroconversion and the earliest time of RNA detection). Notably, these two subjects had quantifiable levels of drug at multiple time points prior to seroconversion, indicating at least intermittent compliance. This observation raises concerns that partial suppression of viral replication could delay the induction and/or maturation of antiviral antibodies to levels necessary for detection by rapid antibody tests. Please provide alternative explanations for these results (e.g., reduced sensitivity of the diagnostic test for specific subtypes of virus, test defect, misuse, or misinterpretation, etc.) along with supporting data, if available.
5. Please identify the rapid anti-HIV-1 rapid antibody and EIA tests that were used in each country that participated in Study CO-US-104-0380.
6. There appears to have been a high degree of discordance in the HIV-1 subtyping assay used in CO-US-104-0380, including different subtype determinations within a single sample when analyzed by HIV-1 protease or reverse transcriptase sequence and, less frequently, when the analysis was conducted between samples collected from the same subject at different time points. Please describe the subtyping assay that was used and comment on the reliability of the technique. If the results are considered reliable, please speculate on possible mechanisms (e.g., recombinant strains, superinfection) and summarize other available data that may help explain the results.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

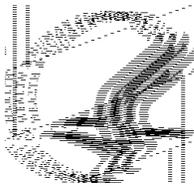
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
04/13/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 6, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Partners PrEP Information Request Regarding Pregnancies

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following request regarding the Partners PrEP datasets is being conveyed to you on behalf of the review team.

Given the datasets you have submitted, please explain how the study team identified:

- The female partner subjects who reported pregnancy (we identified 273 positive pregnancy tests using the LABRES dataset)
- Female subjects who reported multiple pregnancies (we identified 282 subjects in the PREGREP dataset)
- Dates of study drug interruption and treatment resumption (we identified 262 subjects in the PSDILOG)
- Dates of seroconversion in relation to study drug interruption
- Pregnancy outcomes

Alternatively, you may consider submitting an analysis dataset that contains the pregnancy data.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

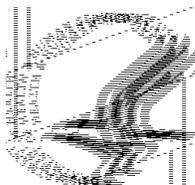
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
04/06/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** April 5, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Clinical Pharmacology Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following request is being conveyed to you on behalf of the review team.

Please confirm if the lower limit of quantification (LLOQ) of tenofovir in plasma was 10 ng/mL for the bioanalytical methods used in both the iPrEx and Partners Prep studies. If the LLOQ is correct, then please clarify why the dataset 'ADCONC' for the Partners Prep study lists numerical values for subjects with plasma concentrations <10 ng/mL, instead of “BQL” (or BLQ, below the limit of quantification). If you determine that these numerical values (<10 ng/mL) should have been BQL, please provide an updated 'ADCONC' dataset with the modified values.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/

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KATHERINE SCHUMANN  
04/05/2012

## Schumann, Katherine

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**From:** Schumann, Katherine  
**Sent:** Tuesday, April 03, 2012 10:35 AM  
**To:** 'Dara Wambach'  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** NDA 21752 S-30 Truvada PrEP - New Clinical Information Request re CDC 4323

Dara,

Please find below an additional information request for NDA 21752 S-30 regarding Study CDC 4232:

For Study CDC 4323, please provide a dataset which includes absolute and percent change from baseline in all BMD parameters (spine, hip, femoral and overall) at one and two years of follow-up for all subjects. In addition, provide a dataset for calculated creatinine clearance (eGFR) for all subjects at every visit. Please submit the requested data by Friday, April 6, 2012, at the latest.

Please let me know if you have any questions.

Warm Regards,

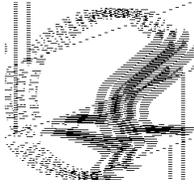
Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: Katherine.Schumann@fda.hhs.gov

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/s/  
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KATHERINE SCHUMANN  
04/03/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** March 30, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP – Comments regarding proposed REMS

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The Agency concludes that there are substantial required revisions to the proposed REMS for Truvada for a PrEP indication (submitted December 14, 2011). The rationale for each revision is included in the comments. See the **Attachment** (REMS document) and Agency comments below. Please note that additional revisions to the REMS document may be forthcoming.

**Required Terminology Revisions**

1. Persons considering or taking Truvada for a PrEP indication are not considered (b) (4), rather they are considered “uninfected individuals” in the context of HIV-1 infection. Based on this rationale, the Agency requires that (b) (4) be replaced with “uninfected individual” throughout the REMS Document and all appended REMS materials including the REMS website.
2. The terminology, (b) (4) must be deleted and replaced with “sexually transmitted infections” (STIs) throughout the proposed REMS and all appended REMS materials including the REMS website. This is a required revision for consistency with the *Interim Guidance for Physicians: CDC Interim Guidance on HIV Pre-Exposure Prophylaxis for Men Who Have Sex with Men*.

3. Different branding and/or packaging is not proposed for TRUVADA for PrEP indication. The text, “(b) (4)”, must be revised to read, “REMS for TRUVADA for a PrEP Indication” throughout the REMS Document, all appended REMS materials, and the REMS website.

## **REMS Document**

### **GOALS**

1. The goals in the proposed REMS for Truvada for a PrEP indication must be revised to align with the revised REMS Elements to ensure that the benefits outweigh the risks of this drug (see the **Attachment**, REMS Document)

### **REMS ELEMENTS**

#### 2. Medication Guide

The Medication Guide will remain as an element in the proposed REMS for Truvada for a PrEP indication. Comments about the Medication Guide will be forthcoming under separate comments from the Division of Antiviral Products.

#### 3. Communication Plan

- a. The Agency concludes that training and education of prescribers for Truvada for a PrEP indication must be ongoing rather than within a finite timeframe of dissemination as defined under a communication plan. Move the following proposed prescriber and uninfected individual educational materials proposed under the communication plan to appear under the Element to Assure Safe Use (ETASU) for prescriber training and education not linked to distribution:
  - Dear Health Care Provider letter
  - Educational Materials for HCPs (*undefined*)
  - Training Guide for Healthcare Providers
  - Full Prescribing Labeling
  - Medication Guide
  - Prescriber Safety Brochure: Important Safety Information about Truvada
  - Individual Safety Brochure: Important Safety Information about Truvada
  - Truvada Wallet Card
  - REMS website ([www.truvadaprep.com](http://www.truvadaprep.com)) Landing page
- b. Remove the Prescriber Knowledge, Attitude and Behavior (KAB) Survey and the Individual KAB Survey from the REMS Document. Neither KAB Survey is required in the materials of a REMS element (in a REMS Document). Though we require that the KAB survey be deleted from the REMS, if Truvada for a PrEP indication is approved, we require that a recruitment communication from you or a vendor be sent to prescribers and uninfected individuals via a separate internet link or by printed copy for access to the Prescriber KAB Survey and the uninfected individual KAB Survey.

- c. The following materials and/or services proposed under the communication plan must be deleted from the proposed REMS for Truvada for a PrEP indication. You may elect to use such materials and/or services outside of a required REMS program.



- d. Move the list of target healthcare prescribers to appear under the ETASU (see **Comment # 4**, below).

4. Element to Assure Safe Use as Prescriber Training and Education

The Agency requires that the proposed ETASU for training and education not be linked to restricted drug distribution. The proposed educational materials directed to prescribers (and for prescribers to use to educate uninfected individuals considering or taking Truvada for a PrEP indication) must appear under this ETASU.

See **Comment # 3. a.**

Additional revisions under this ETASU are:

- a. Revise the list of target healthcare prescribers to include:  
Primary care prescribers (including internal medicine, family practice, and general medicine physicians) infectious disease specialists, emergency medicine physicians, obstetrician-gynecologists, and addiction specialists (see **Attachment**).
- b. Develop and submit information about potential and known safety risks with use of Truvada for a PrEP indication for key professional organizations to disseminate to likely prescribers of Truvada for a PrEP indication. We propose dissemination of this risk information bi-annually for 2 years (see **Attachment**).

6. Timetable for Submission of Assessments

The Timetable for Submission of Assessments must include a 6-month assessment of the number and type of prescriber (by specialty) who completed training and education for Truvada for a PrEP indication and drug-use data for Truvada for a PrEP indication, if approved.

**Required Revisions to Appended REMS Materials including the REMS Website**

7. REMS Website Landing Page ([www.truvadaprep.com](http://www.truvadaprep.com))

a. We require a single-click, direct, prominent link off the *Truvadaprep.com* home web page to a REMS website landing page. For example, the link could state: “Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)”, or “click here for Risk Evaluation and Mitigation Strategy (REMS) information.” You may place this link next to the three links at top of the web page.

b. We require the following language as background information on the REMS landing web page:

“A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

To make sure Truvada for a PrEP indication is prescribed and taken safely, Gilead has worked with the FDA to develop materials for the REMS program to educate and inform healthcare professionals and uninfected individuals at high risk for acquiring HIV-1.”

c. The Agency requires that all references to (b) (4) be deleted from the proposed REMS for Truvada for a PrEP indication (see **Attachment**). Delete the (b) (4) link from your proposed REMS website landing page and all subsequent REMS web pages and appended REMS materials.

d. Delete the following text from the REMS website landing page for Truvada for a PrEP indication:

(b) (4)

8. (b) (4) Site on REMS Website Landing Page

a. The Agency requires that you revise the order of the categories (blue font) listed horizontally at the top of the web page to read in the following order:

- Truvada for PrEP Indication

(b) (4)

- b. You repeat the same Important Safety Information on Truvada on each screen of your REMS website. We require that you only place the Important Safety Information about Truvada on the first page. You may elect to use a link to Important Safety Information for Truvada on subsequent screens, if desired.
- c. Please confirm if the Medication Guide is included in the FDA-Approved Patient Labeling link that appears at the top of the web page.
- d. The Agency requires deletion of the Healthcare Provider and Educator icons (in the upper, far-right margin) from all web pages on the Patient’s website. Revise all references to (b) (4) to “uninfected individual” (see **Required Terminology Revision, Comment # 1**)
- e. Remove the link and list all side effects on the “Side effects can be serious” screen.
- f. On web page 9, remove the (b) (4) link located at the far-right side of the web page.
- g. On web page 18, under “The Importance of Testing”, expand on “getting testing regularly” in accordance with labeling. Under the (b) (4) Section, replace the word (b) (4) with the words ”right away” in the following sentence:

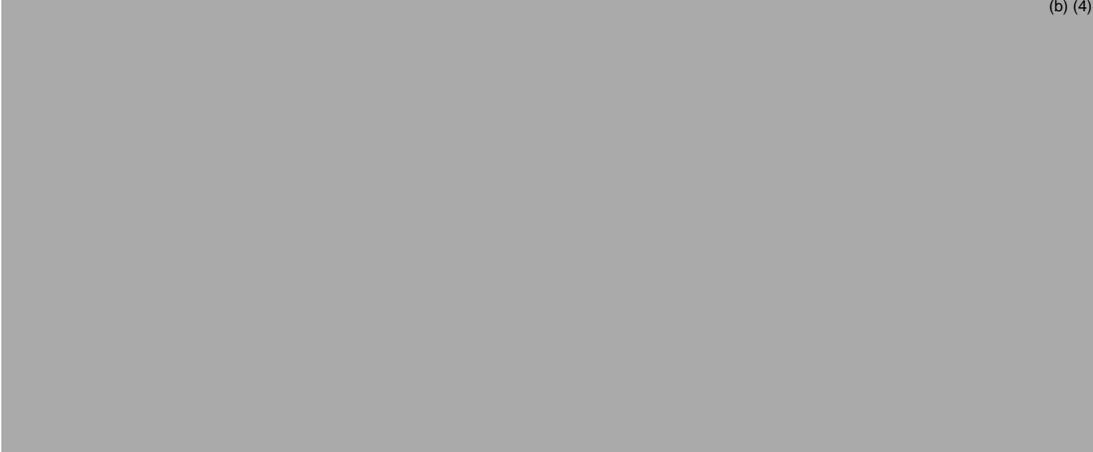
“Tell your healthcare provider immediately if you have any symptoms like feeling tired, fever, sweating a lot, pain, rash, diarrhea, or coughing”

9. (b) (4) on REMS Website Landing Page

See **Comment # 3. c.** above. The (b) (4) site must be removed from the REMS Website landing page and subsequent REMS web pages.

10. Healthcare Provider Site on REMS Website Landing Page

- a. You repeat the same “Important Safety Information including Boxed Warning on Truvada for PrEP” on each screen of your REMS website. We require that you only place the “Important Safety Information about Truvada for a PrEP Indication” on the first web page. You may elect to use a link to “Important Safety Information on Truvada for a PrEP Indication” on subsequent web page screens if desired.
- b. Remove the (b) (4) link from all REMS web pages. See **Comment # 3. c.**
- c. Remove the (b) (4) link located at the far-right side of the web page.
- d. Remove (b) (4) link located at the far-right side of the web page.

e.  (b) (4)

f.

11. Dear Healthcare Provider (DHCP) letter

- a. Revise the DHCP letter to be consistent with revised text in the REMS Document (see **Attachment**). See **Comment # 12** below.

12. Prescriber Safety Brochure

- a. On page 6 of the Prescriber Safety Brochure, delete the sentence: “(b) (4)  
[REDACTED]”

13. (b) (4) Safety Brochure

- a. In the last sentence on page 3 of the Patient Safety Brochure, replace “(b) (4) symptoms” with “unusual symptoms”.
- b. Clarify “adult” on page 6 as an “individual 18 years of age or older”.

14. Training Guide for Healthcare Providers

- a. On page 7 of the Training Guide for Healthcare Providers, delete the same sentence per the above **Comment # 13.a**.
- b. On page 10, include the following header, “Uninfected Individual Counseling” between the top sentence and the header, (b) (4) Should”
- c. On page 12, delete (b) (4) from all appended REMS materials (see **Comment # 3.c**).

15. TRUVADA PrEP Wallet Card

- a. Revise the title of this Wallet Card to be, “TRUVADA for a PrEP Indication”
- b. Remove text that appears above “Healthcare provider: \_\_\_\_\_ and Phone: \_\_\_\_\_”. This same text appears on the reverse side of the Wallet Card.
- c. Remove the website link to (b) (4) from the REMS website
- d. On the wallet card, the side with TRUVADA at the top, in the lower third section of the wallet card, replace the word (b) (4), with the word “every”
- e. Delete the text “(b) (4)  
[REDACTED]”

**Questions, Clarifications and/or Comments for the Applicant**

16. You propose to employ a pharmacy vendor to collect data on the use of TRUVADA for a PrEP indication. Clarify how prescribers of and uninfected individuals taking Truvada for a PrEP indication are proposed to be identified by a pharmacy vendor?
17. You cite “Educational Materials for HCPs” under a proposed communication plan. The placement of “Educational materials for HCPs” is revised to appear under the ETASU (see **Comment 3. a**). Clarify if there are additional prescriber educational materials beyond the “Prescriber Safety Brochure: Important Safety Information about Truvada” and the “Training Guide for Healthcare Providers”. If there are additional proposed prescriber educational materials, such as an educational slide deck, submit these materials to the Agency for review.

### **REMS Assessment Plan**

18. The REMS Assessment Plan must be revised to be consistent with the required revisions to the REMS goals, REMS elements, and appended REMS materials. We require that the REMS Assessment Plan include a 6-month assessment to report on the number and type of prescriber, by specialty, who completed the training and education for Truvada for a PrEP indication and drug-usage data for uninfected individuals taking Truvada for a PrEP indication (See **Comment # 6**).

### **Knowledge, Attitude and Behavior Surveys for Prescribers/Uninfected Individuals**

19. Submit for review the detailed plan you propose to use to evaluate prescriber and uninfected individual knowledge about the safe use of Truvada for a PrEP indication, if approved. You may submit the proposed plan after approval of the REMS; however, submit this plan at least 90 days before you conduct the evaluation. Code this submission "REMS Correspondence." If you plan to conduct the required assessment using a survey, you must submit all methodology (design, conduct, and interpretation of the findings) and instruments to be used to evaluate knowledge about the risks associated with and safe use of Truvada for a PrEP indication, if approved.

### **REMS Supporting Document**

20. We remind you that the REMS Supporting Document must be consistent with all required revisions to the REMS Document.

### **General Comments**

**Resubmission Requirements and Instructions:** Submit the revised proposed REMS for Truvada for a PrEP Indication with all appended REMS materials including the REMS website landing page and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all (each) revised appended material and document. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

**Format Request:** Submit your proposed REMS and other appended REMS materials in MS Word format. It makes review of these materials more efficient and easier for the web posting staff to make the document 508 Compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. However, to efficiently work in each document, we request a separate WORD document for each appended material. If certain documents are only in PDF format, they may be submitted as such, but the Agency's preference is to include as many as possible in a single MS Word document.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

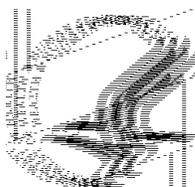
Attachment: REMS document

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KATHERINE SCHUMANN  
03/30/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** March 29, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following requests are being conveyed to you on behalf of the review team.

Comments 1-6 refer to Study GS-US-104-0288 (iPrEx):

**Clinical Virology**

1. Please verify that the pharmacokinetic (i.e., PKDT) and RNA sampling dates of the iPrEx datasets (e.g., DERRESI) are equivalent. If not, please provide the date/DAY of sample collection for both the PK and RNA assays.
2. Please verify that a value of “40” copies/mL in the “OTHERCOP” column of the DERRESI dataset indicates a negative result (i.e., below the lower limit of quantification and with no HIV-1 RNA detected by RT-PCR).
3. Please include data from the 10 subjects (2 FTC/TDF and 8 Placebo) who were seronegative at enrollment but subsequently determined to be infected at baseline by RT-PCR in the DERRESI file.
4. It is unclear if the time to infection (TTINF in the DERRESI dataset) of the iPrEx trial was defined by the earliest detected HIV-1 RNA or by the time of seroconversion. Please provide

the dates of seroconversion (e.g., concordant rapid tests or discordant rapid tests with confirmatory EIA, WB, or RT-PCR) if different from those associated with earliest detectable HIV-1 RNA.

5. In Supplementary Figure 4 of Grant et al., 2010 (N Engl J Med. Dec 30;363(27)2587-99), the authors indicate that plasma RNA levels at the seroconversion visit were comparable between subjects treated with FTC/TDF or placebo. Please provide those data and a description of the analysis.

### **Biostatistics**

6. According to the SAS dataset BASICS, using a stop date of July 31, 2010, there are 78 infections in the placebo group out of 1218 eligible subjects and 45 infections in the FTC/TDF group out of 1224 eligible subjects. Please concur that these are the numbers you will be using in your Advisory Committee presentation and in the label. Otherwise, provide an explicit algorithm in English, not in SAS code, for obtaining different results using the dataset BASICS.

### **Clinical**

7. Please provide the Subject ID listings for all subjects in Study CDC 4323 with > 5% decrease from baseline in BMD in the DEXA substudy.
8. Please provide a subject narrative for the subject in Study CDC TDF2 who was found to have high levels of K65R, M184V, and A62V reverse transcriptase resistance mutations in the FTC/TDF group. Indicate treatment course, including dates of study drug initiation, study drug discontinuation, HIV seroconversion, and confirmation testing of HIV infection.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/

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KATHERINE SCHUMANN  
03/29/2012

## Schumann, Katherine

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**From:** Schumann, Katherine  
**Sent:** Sunday, March 25, 2012 9:43 AM  
**To:** 'Dara Wambach'  
**Cc:** 'Regulatory Archives'; Paul Tomkins  
**Subject:** NDA 21752 S-30: Additional Questions for Clarification Re: CO-US-104-0288

Dear Dara,

The review team for NDA 21752 S-30 has the following questions for clarification regarding Study CO-US-104-0288:

In the CSR Addendum for Study CO-US-104-0288, you state that the following 4 subjects tested positive for HIV infection between 21 November 2010 and 28 February 2011: 8730001, 8831678, 8944264, and 8730679. Yet, the first three of these subjects at least are counted as on-treatment events in the mITT analysis conducted by UCSF and Gilead (Subject Listing 4.1.4). Please clarify when these 4 subjects seroconverted in relation to the 21 November 2010 cutoff date.

In addition, please confirm that the following 4 subjects seroconverted after the 21 November cutoff date and thus are to be excluded from the mITT analysis of seroconversion events Up to End of Treatment (July 31, 2010) and Up to End of Treatment plus 8 weeks (November 21, 2010) - the UCSF approach to the efficacy analysis:

9051473	Placebo
9635703	Placebo
9433201	TDF/FTC
9635239	TDF/FTC

For Gilead's analysis of events, please indicate which variables were used to derive dates of seroconversion and dates of study drug discontinuation.

Please clarify why the same population totals were used for the mITT and ITT analyses as the randomization total (2499: TDF/FTC 1251, placebo 1248) as noted in Table 4-1 of the CSR Addendum.

A response via email is sufficient. Please let me know if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: Katherine.Schumann@fda.hhs.gov

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/s/  
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KATHERINE SCHUMANN  
03/26/2012

## Schumann, Katherine

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**From:** Schumann, Katherine  
**Sent:** Friday, March 23, 2012 12:28 PM  
**To:** 'Dara Wambach'  
**Cc:** 'Regulatory Archives'; Paul Tomkins  
**Subject:** NDA 21752 S-30 - Question Regarding Subject IDs

Dear Dara,

The review team for NDA 21752 S-30 has one question for you regarding the iPrEx trial.

They have noted that you performed a sensitivity analysis of efficacy by excluding Truvada subjects who stopped study drug but stayed on study. Four subjects who converted met this definition and were excluded. Can you provide the subject IDs for those four subjects in the iPrEx trial?

An informal response via email is sufficient.

Warm Regards,

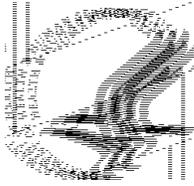
Katie

Katherine Schumann, M.S.  
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/s/  
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KATHERINE SCHUMANN  
03/26/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** March 21, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

The following request is being conveyed to you on behalf of the review team.

DAVP would like to request pharmacokinetic data recently reported at CROI from a clinical study titled "Strand Study." The Strand Study was conducted by Peter Anderson et al., and aimed to evaluate the concentrations of tenofovir in plasma and PBMCs after several different dosing regimens with Truvada. Twenty-four healthy subjects were given Truvada for six weeks using a dosing frequency of either 2-times, 4-times, or 7-times per week (once daily dosing). Study results showed that Truvada dosing regimens of 2-times, 4-times, and 7-times per week produced median intracellular tenofovir concentrations of 11, 32, and 42 fmol/M viable cells, respectively. The plasma concentrations of tenofovir were not reported.

If it is possible for you to obtain these data, we request the following information from the Strand Study:

- Individual subject pharmacokinetic data collected in plasma and PBMCs.
- Statistical summaries of all pharmacokinetic parameters for tenofovir.
- Time of blood sampling relative to last time of drug dose.
- Observed or self-reported medication adherence data.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

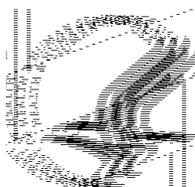
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
03/21/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** March 7, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of March 1, 2012, received March 2, 2012, containing responses to our information request of February 23, 2012.

The following requests concerning Study CO-US-104-0380 are being conveyed to you on behalf of the review team.

1. Please explain why the deaths of Subjects 5137810 and 5221015, both of whom are in the TDF treatment group and included in the ITT population, were not reported in the CSR listing of partner subject deaths (Section 11.3).
2. You identify 6 subjects as having discontinued study drug due to adverse event (all for increased blood creatinine). We have identified, however, an additional subject who appears to have permanently discontinued study drug due to the adverse event of esophageal carcinoma (Subject 5520516 - placebo group). Please explain why this subject was excluded from your listing.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

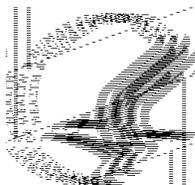
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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
03/07/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** February 23, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of February 10, 2012, received February 13, 2012, containing responses to our information request of January 20, 2012.

We have the following request regarding Study US-CO-104-0380.

Please provide a summary of subject disposition that includes the proportion of subjects per treatment arm that were still on study or had completed study as of the July 10, 2011 cutoff date, as well as those that had terminated the study early (broken down by reasons for termination). In your summary, also indicate the proportion of subjects who discontinued study early for reasons related to adverse event.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
02/23/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 21752 BLA#	NDA Supplement #:S-30 BLA STN #	Efficacy Supplement Type SE- 1
Proprietary Name: Truvada Established/Proper Name: emtricitabine/tenofovir disoproxil fumarate (fixed-dose combination) Dosage Form: tablet Strengths: 200mg/300mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: December 14, 2011 Date of Receipt: December 15, 2011 Date clock started after UN:		
PDUFA Goal Date: June 15, 2012		Action Goal Date (if different):
Filing Date: January 14, 2012		Date of Filing Meeting: January 5, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication: for pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 108,930 / 52,849 / 67,671 / 53,971 / 71,859 / 75,365				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			X																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  <i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		X																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?		X		No change in product.
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC RPM notified.
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>	X			Consult sent.
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		Not necessary per discussion between K. Marcus, D. Birnkrant, J. Murray
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		Type C meetings held February 24, 2009 and October 28, 2009. Minutes distributed prior to filing meeting.

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> December 8, 2010  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 5, 2012

**BLA/NDA/Supp #:** 21752 S-030

**PROPRIETARY NAME:** TRUVADA

**ESTABLISHED/PROPER NAME:** emtricitabine/tenofovir disoproxil fumarate

**DOSAGE FORM/STRENGTH:** Tablets 200 mg / 300 mg

**APPLICANT:** Gilead Sciences Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** new indication for pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1

**BACKGROUND:** In February 2009, DAVP and Gilead began discussing the trials being conducted under IND with Truvada/Viread for PrEP and the data needed to support this new indication, to ensure proper labeling and use of the product(s). A pre-NDA meeting was held in December 2010 to discuss the iPrEx data to support a supplemental NDA.

In May 2011, DAVP facilitated a CDER Regulatory Briefing to discuss the feasibility of implementing a REMS with ETASU to link access to the drug to HIV testing. It was generally agreed that such a restriction would not be an effective strategy for risk mitigation.

In July 2011, following the release of positive interim data from the University of Washington Partners PrEP trial, DAVP asked Gilead to include this additional data to support a broader population for the PrEP indication.

In December 2011, Gilead submitted this supplemental application to support a new indication for Truvada for pre-exposure prophylaxis of HIV-1 (PrEP).

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Katherine Schumann	Y
	CPMS/TL:	Victoria Tyson	N
Cross-Discipline Team Leader (CDTL)	Kendall Marcus		Y
Clinical	Reviewer:	Peter Miele	Y
	TL:	Linda Lewis	Y

Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Damon Deming	Y
	TL:	Jules O'Rear	N

Clinical Pharmacology	Reviewer:	Ruben Ayala	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Thomas Hammerstrom (Susan Zhou attended)	N
	TL:	Greg Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pritam Verma	N
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Stephen Miller	Y
	TL:	Tom Oliver	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:	Kendra Worthy	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Tony El-Hage	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Edward Cox, Office Director, OAP David Roeder, ADRA, OAP Debra Birnkrant, Director, DAVP Jeffrey Murray, Deputy Director, DAVP Karen Winestock, CPMS, DAVP Stacey Min, Acting CPMS, DAVP Paul Tran, DFO, DACCM		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date if known: May 10, 2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><b><i>If no, for an original NME or BLA application, include the reason. For example:</i></b></p> <ul style="list-style-type: none"> <li>○ <b><i>this drug/biologic is not the first in its class</i></b></li> <li>○ <b><i>the clinical study design was acceptable</i></b></li> <li>○ <b><i>the application did not raise significant safety or efficacy issues</i></b></li> <li>○ <b><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></b></li> </ul>	<p>Reason:</p>
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> A request was sent to the sponsor to update the environmental assessment to take into account the increase in use that may be estimated based upon the approval of this new indication.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b> No product quality changes.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Debra Birnkrant, MD, Director, DAVP</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  Filing Date: February 13, 2012  PDUFA Date: June 15, 2012</p> <p>Comments:</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p>Review issues were communicated to the applicant in a correspondence dated January 20, 2012, and repeated in the 60-day filing letter dated February 13, 2012.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
<p><b>ACTIONS ITEMS</b></p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product</p>

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Katherine Schumann

Regulatory Project Manager

Date

Victoria Tyson

Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

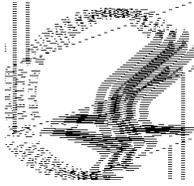
If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/  
-----

KATHERINE SCHUMANN  
02/21/2012

VICTORIA L TYSON  
02/21/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** February 15, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. Please also refer to your submission of February 10, 2012, received February 13, 2012, containing responses to our information request of January 20, 2012.

We have the following comments regarding the subject disposition for Study US-CO-104-0288, as described in the CSR addendum.

- I. Using the TERMRSN variable in the BASICS dataset, we calculate that 1886 (75%) subjects completed the trial and 613 subjects (25%) discontinued the trial prematurely. In Table 3-1, you list subjects who permanently discontinued study drug. It appears that some of these subjects remained in the trial through completion (while not taking study medication), while others terminated the trial early. The reasons listed for early trial termination do not include Adverse Events as a category, yet it should be considered that some subjects who discontinued study drug due to AEs may have also dropped out of the trial for the same reasons (e.g. Subject 9313084) and are not being accurately captured by the given TERMRSN categories.
  1. Please re-construct your disposition table to reflect the number of subjects who completed the trial and the number who discontinued early as of the November 21, 2010 cut-off. It is presumed that the group of subjects who permanently discontinued study drug will constitute subsets of the above two categories. Therefore, indicate how

many subjects permanently discontinued study medication but remained on trial through completion and how many of these subjects terminated the trial early.

2. If subjects currently categorized as terminated for reasons other than adverse event have been incorrectly categorized as “Investigator Decision”, “Participant Refused” or “Other”, re-categorize the subject and use the revised reason to construct the disposition table requested above.
  3. Please provide the subject ID of any subject who has been re-categorized and the revised disposition.
  4. Submit a summary for all subjects who terminated the trial early for the category of “Investigator Decision”. In your summary, describe the reasons provided for “Investigator Decision”.
  5. Compile a list of reasons provided for subjects who terminated the trial early for the category of “Participant Refused”.
  6. Compile a list of reasons provided for subjects who terminated the trial early for the category of “Other”.
- II. It is not clear from the CSR addendum, exactly how many subjects permanently discontinued study drug due to an AE.

Section 3.1, page 14, and Table 3-1, states that:

“Ninety-nine subjects (48 [4%] FTC/TDF, 51 [4%] placebo) permanently discontinued the study due to a clinical AE or laboratory toxicity through the 21 November 2010 cutoff date”

While Section 5.5, page 44, and Table 5-2, indicates that there were 97 such subjects:

“ ..... permanently discontinued study drug due to a clinical AE or laboratory AE at the time of the 21 November 2010 data cutoff for the complete double-blind analysis (83 subjects due to clinical AE and 14 subjects due to laboratory AE).....”

Per our analysis, we calculate 97 subjects who permanently discontinued study drug due to a treatment-emergent AE (using the derae.xpt 09Feb2012 dataset - CRF Plate 240).

Please clarify these seeming contradictions in the CSR.

We have the following request regarding the BASICS dataset submitted February 10, 2012:

- III. Please clarify the LASTBIN variable (Last Date of Exposure). The data entered do not appear to be dates. Since the EXPOSURE variable is dependent on the LASTBIN information, please verify that the EXPOSURE data is accurate.

We have the following questions regarding the new datasets submitted for Study US-CO-104-0380.

- IV. In the dataset KEYVARS, there are 2 placebo subjects, 5 tenofovir subjects and 4 FTC/TDF subjects who are not considered in the modified ITT dataset but who are not infected at enrollment. Their history of HIV measurements, as recorded in the dataset ADHIV is as follows:

MITT=0						
PTID	STUDYDAY	DTENROLL	DTVISIT	HIVITT	HIVPRIM	HIVSITE
5206718	22	26FEB2009	20MAR2009	0	0	0
5345919	.	.	.	.	.	.
5400210	10	08JUL2008	18JUL2008	0	0	0
5400912	28	30JUL2008	27AUG2008	0	0	0
5419919	15	05MAY2009	20MAY2009	0	0	0
5509716	28	12FEB2009	12MAR2009	0	0	0
	55	12FEB2009	08APR2009	0	0	0
	82	12FEB2009	05MAY2009	0	0	0
	110	12FEB2009	02JUN2009	0	0	0
5518111	28	20MAY2009	17JUN2009	0	0	0
	57	20MAY2009	16JUL2009	0	0	0
	84	20MAY2009	12AUG2009	0	0	0
	112	20MAY2009	09SEP2009	0	0	0
	140	20MAY2009	07OCT2009	0	0	0
	168	20MAY2009	04NOV2009	0	0	0
	196	20MAY2009	02DEC2009	0	0	0
	224	20MAY2009	30DEC2009	0	0	0
	252	20MAY2009	27JAN2010	0	0	0
	280	20MAY2009	24FEB2010	0	0	0
	308	20MAY2009	24MAR2010	0	0	0
	335	20MAY2009	20APR2010	0	0	0
5518314	24	22MAY2009	15JUN2009	0	0	0
	56	22MAY2009	17JUL2009	0	0	0
	84	22MAY2009	14AUG2009	0	0	0
	112	22MAY2009	11SEP2009	0	0	0
	139	22MAY2009	08OCT2009	0	0	0
5527717	212	12AUG2009	12MAR2010	0	0	0
5716913	15	14MAY2009	29MAY2009	0	0	0
5717514	9	20MAY2009	29MAY2009	0	0	0

Please explain exclusion of these subjects from the MITT dataset. They all have measurements on drug (except for 5345919) and none are infected at the start or at the end.

- V. There are 10 placebo subjects, 7 tenofovir subjects and 8 FTC/TDF subjects with no measurements of HIV while on drug but who are considered in the MITT dataset. However, their variables ITTHIV and PRIMHIV in the KEYVARS dataset are missing. Please explain the inclusion of these subjects in the MITT dataset.

These are the subjects:

ARMNAME	PTID	
FTC/TDF	5018513	
	5307413	
	5319716	
	5328317	
	5348416	
	5515715	
	5550712	
	5638015	
	Placebo	5127516
		5344018
5429418		
5435414		
5516116		
5519712		
5545516		
5613718		
5617416		
5623515		
TDF	5055016	
	5124011	
	5148516	
	5439417	
	5610116	
	5651218	
5713512		

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
02/15/2012



NDA 21752/S-030

**FILING COMMUNICATION**

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/tenofovir disoproxil fumarate) 200 mg and 300 mg.

We also refer to your submissions dated January 11, 2012, January 23, 2012, February 3, 2012 and February 10, 2012.

This supplemental application proposes the following change: a new indication for the use of TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets for pre-exposure prophylaxis of HIV-1 infection (PrEP).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 15, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 25, 2012.

During our filing review of your supplemental application, we identified several potential review issues, communicated to you in our correspondence dated January 20, 2012, and listed below:

**Clinical:**

1. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.
2. The MEDRAPT columns in the CO-US-104-0288 AE datasets and the MEDTERM 1 column in the CO-US-104-0380 AE dataset appear to include PT, SOC and LLT terms all within the same entry field. To facilitate review of the safety endpoints, different MedDRA terms should be separated into individual columns for each reported AE, one entry per column, with appropriate column headers. In addition, include start and stop dates for study drug and a flag indicating whether the subject was taking study drug at the time of AE.
3. Please indicate which version of MedDRA was used to code AEs in CO-US-104-0380.
4. All datasets should include a column identifying the treatment arm for each subject.
5. Please confirm that the datasets included in the CO-US-104-0288 addendum contain cumulative data from enrollment through the November 1, 2010 cut-off and thus encompass all of the data presented in the primary analysis datasets. In addition, please clarify the distinction between datasets with a July 29, 2011 cut-off and those with a September 09, 2011 cut-off included in the addendum.
6. Please indicate which dataset(s) were used to generate Table 1.1.1.1 in the CO-US-104-0288 CSR. Similarly, indicate which dataset(s) were used to generate Figures 8-1 and 8-2 in the CO-US-104-0380 CSR, since the report indicates that pre-existing tables were used from the DSMB closed report
7. Please provide analysis datasets for laboratory testing for each study, CO-US-104-0288 and CO-US-104-0380, that includes:
  - a) Subject ID
  - b) Treatment assignment
  - c) Date of lab test
  - d) Study Day
  - e) Lab test code
  - f) Lab category (hematology, chemistry, coagulation, viral load, lipids, etc.)
  - g) Baseline lab value
  - h) Date of baseline lab value
  - i) Lab test result in standard units
  - j) Unit of measurement
  - k) Reference range lower limit
  - l) Reference range upper limit

- m) Reference range indicator for lab test result: normal, high, low
- n) Change from baseline value
- o) Toxicity Grade (DAIDS)
- p) Visit Number or Study Week
- q) Visit name: Screening, Baseline, Treatment, Follow-up, etc.
- r) Flag indicating whether subject was taking study drug at time of lab test
- s) Drug start date
- t) Drug stop date

**Biostatistics:**

8. Please submit analysis datasets in SAS transportable files for CO-US-104-0288 and CO-US-104-0380 which contain the following:
  - a. Demographic and baseline data with one record per patient. The data should include at least the following fields based on the CO-US-104-0288 results.
    - Patient ID, as a numeric variable
    - Treatment assignment
    - Country, spelled out as a short (e.g. 10 letter) word
    - Site within country
    - Race, spelled out as a short word and limited to the possibilities: White, Black, Asian, Mixed
    - Ethnicity (Hispanic or not)
    - Education
    - Risk at Screening
    - Daily alcohol use
    - HSV-2 at screening
    - Circumcised
    - Age at entry
    - Analysis population indicators (ITT, mITT, PP, safety)
    - Other key variables
  - b. Longitudinal HIV-1 visit data with one record per visit per patient and including at least the following fields:
    - Patient ID
    - Treatment assignment
    - Date of first use of study drug
    - Date of current visit
    - Study day of current visit
    - Results of HIV test

All dates should be numeric or in SAS date formats.

- c. Important covariates selected for subgroup analyses, including at least adherence data (i.e., % of pill use in CO-US-104-0288). If the adherence data are collected on a different schedule from HIV tests, then also include a dataset with one record per date at which adherence were collected per patient and organized similarly to the dataset containing visit by visit date about HIV tests.
  - d. The analysis datasets for CO-US-104-0380 should be changed according to the study design and efficacy findings.
9. Please clarify whether data for trial CO-US-104-0288 come from the file labeled 288 or from the file labeled 288\_addendum. The required datasets and all source input datasets used for the generation of the required datasets should be submitted to the CDER EDR. SAS programs for the generation of the new datasets should be provided.
  10. Please clarify the relationship between the variables HIVSTAT, RESULTS1 and RESULTS2 in the dataset HIV for trial CO-US-104-0288. Please explain what 0 means as a value for these variables (e.g. not recorded).
  11. Please provide any data on adherence to condoms by visit for both trials. If available, such data should include a variables measuring how many times condom protected sex occurred since the previous visit and how many times condom unprotected sex occurred since the previous visit.

**Clinical Virology:**

12. Please submit a line-item virology dataset that consolidates pharmacokinetic and virologic data. Specifically, the file should allow for the comparison of drug concentrations, virus titers, and genotypic data of samples collected at, or near, the same time point(s). We request that the file include the following data:
  - Subject ID
  - Trial (i.e., iPrEx or Partners PrEP)
  - Cohort
  - Time of seroconversion (Days from Baseline)
  - HIV-1 subtype
  - Time of PK Sample Collection (Days from Baseline)
  - TFV concentration
  - TFV-DP concentration
  - FTC concentration
  - FTC-TP concentration
  - Time of virology sample collection (Days from Baseline)
  - HIV-1 RNA load
  - Genotypic data (complete HIV-1 RT amino acid sequence: if deep sequencing was used, provide a consensus amino acid sequence, identify variants that

occurred in more than 1 individual and their percent within an individual's population); blank cells should be used for positions matching reference RT sequence (see guidance on submission of HIV-1 resistance data). Provide a separate dataset for allele-specific RT-PCR.

- Genotypic data of the Index Subject if resistance-associated substitutions are identified in the Partner Subject (if available from Partners PrEP). Include an identifier for matching with the appropriate partner and a column with “Y” or “N” as to whether a phylogenetic comparison of the index and partner viruses indicates that the partner was the probable source of the subject's infection.

Multiple rows may be included for the same subject if samples collected at multiple time points were evaluated. Also, please identify the assays used for RNA load determination and genotypic data analysis (e.g., allele-specific, ultra-deep, or population-based nucleotide sequencing assay).

13. Please provide study reports for the phenotypic and genotypic studies that were conducted for each trial, including detailed methodologies and a description of the performance parameters of assays that have not been approved. The assay descriptions should include primer and probe sequences (when applicable), a description of the sensitivity limits for minority populations, and—in the case of allele-specific RT-PCR—the detection limits for each of the degenerate bases within a codon for each resistance-associated substitution that was evaluated).
14. Please conduct an expanded HIV-1 resistance analysis for subjects who failed prophylaxis and had detectable drug levels or who were missing those pharmacokinetic data. The analysis should include a genotypic characterization of reverse transcriptase using an assay that is sensitive to minority species (e.g., 454 sequencing) and a phenotypic characterization for emtricitabine and tenofovir susceptibility if no known resistance-associated substitutions are identified.

**Clinical Pharmacology:**

15. Please submit all available method validation reports and bioanalytical study reports for both Phase 3 studies used in the analysis of tenofovir and emtricitabine concentrations in plasma and PBMCs.
16. If available, please provide the time of blood sampling (for analysis of plasma and PBMC drug concentrations) relative to the approximate time of the previous dose of study drug for all subjects (based on direct observation or self-reporting) from whom you collected samples in both Phase 3 studies. Please include this information as a separate data column in the DRUGORIG and DRUGLVL datasets. As an alternative, you may include this information in the consolidated PK and virology dataset(s) as described in the Clinical Virology request above.

We provided the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not

indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

We acknowledge receipt on February 13, 2012, of your submission that consists of your response to the potential review issues listed above. This submission is currently under review.

While we anticipate that any future responses to requests for information that are submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

## **LABELING**

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. On the first page of the package insert, please add the route of administration after the product title, as follows:

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use

2. At the end of the Highlights section, please word the reference to Section 17 as follows:

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

3. Directly under the heading 17 PATIENT COUNSELING INFORMATION, please word the reference to the Medication Guide as follows:

See FDA-approved patient labeling (Medication Guide)

We request that you resubmit labeling that addresses these issues by March 2, 2012. The resubmitted labeling will be used for further labeling discussions.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission 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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **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 acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Katherine Schumann, 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

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/s/

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DEBRA B BIRNKRANT  
02/13/2012

**Schumann, Katherine**

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**Sent:** Friday, February 10, 2012 10:35 AM  
**To:** 'Dara Wambach'  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** RE: NDA 21-752/S-30 - Partners PrEP Clinical Study Report

Dara,

I am still waiting for a reply regarding your proposal below, but in the meantime, I have received the following request from the clinical virology reviewers:

In addition to an updated resistance dataset, please have the sponsor send an additional dataset containing the initial and revised line listings for all subjects who had any data changes.

Please let me know if you have any questions.

Warm Regards,

Katie  
(301) 796-1182

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**From:** Dara Wambach [mailto:Dara.Wambach@gilead.com]  
**Sent:** Thursday, February 09, 2012 4:56 PM  
**To:** Schumann, Katherine  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** NDA 21-752/S-30 - Partners PrEP Clinical Study Report

**RE: NDA 21-752/S-30 - Partners PrEP Clinical Study Report**

Dear Katie,

During the process of responding to the Agency's request for biostatistics and clinical virology information of 20 January 2012, the Partners PrEP Study Team have identified a few errors in the safety, laboratory and resistance tables of the CSR which we wish to bring to the FDA review team's attention. Gilead and the Partners PrEP team have discussed the impact of the errors and agree that impact on the CSR is minimal and that there are no changes in the interpretation of the data.

A full description of the errors from the Partners PrEP study team is attached, along with a WORD version of the CSR showing all of the changes indicated by the corrections. To assure that the datasets and in-text tables are aligned with one another, Gilead is preparing an amendment to the CSR for submission to NDA 21-752/S-030 within the next 14 days.

The key corrections are summarized as follows:

1. A coding error that excluded a post-baseline creatinine or phosphorus measurements if only a single measurement was recorded for the visit date. The incorrect code only selected the data if values for both parameters were recorded on a single visit date. A similar coding error led to exclusion of bilirubin levels on some visit dates.
2. As per the SAP all graded laboratory events required a second confirmation test. If the event grade was lower on the second test, the lower grade should be confirmed. A coding error incorrectly selected for the grade, ie Grade 3 of the initial measurement, even if the second measurement was a lower grade, ie Grade 2. Therefore, some events should have been reported at a lower grade than in the original CSR.
3. Based upon re-review with the virology laboratory, HIV for two seroconverters identified in the CSR as having a non-primary mutations (T215C and K 65N) were confirmed to be wild-type instead.

As noted above, an amendment to the CSR is in preparation with anticipated submission timing within 14 days. Gilead would appreciate the Agency's endorsement of this plan.

If it would be helpful, we are available to discuss this issue via teleconference on Friday, 10 February, or early next week.

Kind regards,  
Dara

Dara Wambach, MA  
Associate Director, Regulatory Affairs  
Gilead Sciences  
333 Lakeside Drive  
Foster City, CA 94404  
ph: 650-522-5163  
fax: 650-522-5489  
email: [dara.wambach@gilead.com](mailto:dara.wambach@gilead.com)

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/s/

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KATHERINE SCHUMANN  
02/10/2012

**Schumann, Katherine**

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**From:** Dara Wambach [Dara.Wambach@gilead.com]  
**Sent:** Tuesday, January 31, 2012 12:55 PM  
**To:** Schumann, Katherine  
**Cc:** Regulatory Archives; Paul Tomkins  
**Subject:** RE: NDA 21752 S-30 Truvada PrEP - Question regarding iPrEx data  
**Follow Up Flag:** Follow up  
**Flag Status:** Completed  
**Attachments:** 2012\_01\_27 NDA 21752 S-30 Information Request.pdf

**RE: NDA 21752 S-30 Truvada PrEP - Question regarding iPrEx data**

Dear Katie,

Gilead confirms that when the Demog page of the CRF was modified by the study team (Panel 005 to Panel 006) the education field was deleted. However, data regarding education were collected via the Computer Assisted Structured Interview (CASI) for which there is no CRF. This information is currently being incorporated into the analysis datasets in preparation for the response to the Agency's 20 January 2012 Request for Information.

Table 8-4 from the CSR was derived from Table 1 in the NEJM publication which incorporated the information from the CASI.

Please let us know if additional clarity is needed. As noted above, the revised analysis datasets planned for submission on 10 February 2012 will incorporate the education levels for all of the subjects in the study.

Kind regards,  
Dara

Dara Wambach, MA  
Associate Director, Regulatory Affairs  
Gilead Sciences  
333 Lakeside Drive  
Foster City, CA 94404  
ph: (650) 522-5163  
fax: (650) 522-5489  
[dara.wambach@gilead.com](mailto:dara.wambach@gilead.com)

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**From:** Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]  
**Sent:** Friday, January 27, 2012 11:58 AM  
**To:** Dara Wambach  
**Subject:** NDA 21752 S-30 Truvada PrEP - Question regarding iPrEx data

Hi Dara,

Please find attached a correspondence containing a question from the review team regarding the iPrEx data.

Let me know if you have any questions.

Thanks,

Katie

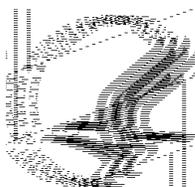
Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP

Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: Katherine.Schumann@fda.hhs.gov

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KATHERINE SCHUMANN  
01/31/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** January 27, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets. The following request for information is being conveyed to you on behalf of the review team:

Regarding CO-US-104-0288, the DEMO.xpt dataset(s) and the derived analysis dataset(s), BASICS.xpt submitted on 1/20/2012, appear to use the DEMOGRAPHICS CRF's (DFPLATE) 005 (Version 1.0 - Peru and Ecuador) and 006 (Version 4.0 - Brazil, US, S. Africa, Thailand) to generate baseline education level data (variable EDUCATE). However, CRF 006 does not elicit education information. Therefore, for 1445 subjects in the ITT population, the EDUCATE variable in the DEMO datasets is blank. Was data regarding baseline education level obtained for these 1445 subjects? If so, please indicate where this information can be found. Table 8-4 of the iPrEx study report (May 1, 2010 cut-off) suggests such data is available for all 2499 subjects:

Education Level - no. (%)	p = 0.26		
Less than Secondary		244 (20)	279 (22)
Completed Secondary		453 (36)	430 (34)
Post-Secondary		539 (43)	525 (42)
No Answer/Missing		12 (1)	17 (1)

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/

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KATHERINE SCHUMANN  
01/27/2012

**From:** Schumann, Katherine  
**Sent:** Monday, January 23, 2012 3:44 PM  
**To:** 'Dara Wambach'  
**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-030 - dataset question  
Hi Dara,

We received the submission to NDA 21752 S-30 made on Friday with the iPrEx analysis datasets. Thanks very much for sending them. I now have a question from one of the reviewers regarding the contents of the submission:

In the folder of recently submitted analyses datasets for iPrEx, there is a transport file, adlb.xpt, that is empty. It is not described in the define.pdf file either. Could you clarify whether it is a mistake, and confirm that it is supposed to be empty?

Could you check with your team and let me know about this particular transport file? Thanks!

Warm Regards,

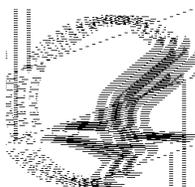
Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: Katherine.Schumann@fda.hhs.gov

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KATHERINE SCHUMANN  
01/23/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** January 20, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

---

Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate) tablets.

In our preliminary assessment of your submission package, we have identified the following issues that may impede the conduct of a substantive and timely review. Some of these issues may be addressed in the analysis datasets you plan to submit. For those that are not, please submit your response to our requests within 21 days.

**Clinical:**

1. The MEDRAPT columns in the CO-US-104-0288 AE datasets and the MEDTERM 1 column in the CO-US-104-0380 AE dataset appear to include PT, SOC and LLT terms all within the same entry field. To facilitate review of the safety endpoints, different MedDRA terms should be separated into individual columns for each reported AE, one entry per column, with appropriate column headers. In addition, include start and stop dates for study drug and a flag indicating whether the subject was taking study drug at the time of AE.
2. Please indicate which version of MedDRA was used to code AEs in CO-US-104-0380.
3. All datasets should include a column identifying the treatment arm for each subject.
4. Please confirm that the datasets included in the CO-US-104-0288 addendum contain cumulative data from enrollment through the November 1, 2010 cut-off and thus encompass

all of the data presented in the primary analysis datasets. In addition, please clarify the distinction between datasets with a July 29, 2011 cut-off and those with a September 09, 2011 cut-off included in the addendum.

5. Please indicate which dataset(s) were used to generate Table 1.1.1.1 in the CO-US-104-0288 CSR. Similarly, indicate which dataset(s) were used to generate Figures 8-1 and 8-2 in the CO-US-104-0380 CSR, since the report indicates that pre-existing tables were used from the DSMB closed report
6. Please provide analysis datasets for laboratory testing for each study, CO-US-104-0288 and CO-US-104-0380, that includes:
  - a) Subject ID
  - b) Treatment assignment
  - c) Date of lab test
  - d) Study Day
  - e) Lab test code
  - f) Lab category (hematology, chemistry, coagulation, viral load, lipids, etc.)
  - g) Baseline lab value
  - h) Date of baseline lab value
  - i) Lab test result in standard units
  - j) Unit of measurement
  - k) Reference range lower limit
  - l) Reference range upper limit
  - m) Reference range indicator for lab test result: normal, high, low
  - n) Change from baseline value
  - o) Toxicity Grade (DAIDS)
  - p) Visit Number or Study Week
  - q) Visit name: Screening, Baseline, Treatment, Follow-up, etc.
  - r) Flag indicating whether subject was taking study drug at time of lab test
  - s) Drug start date
  - t) Drug stop date

**Biostatistics:**

7. Please submit analysis datasets in SAS transportable files for CO-US-104-0288 and CO-US-104-0380 which contain the following:
  - a. Demographic and baseline data with one record per patient. The data should include at least the following fields based on the CO-US-104-0288 results.
    - Patient ID, as a numeric variable
    - Treatment assignment
    - Country, spelled out as a short (e.g. 10 letter) word
    - Site within country
    - Race, spelled out as a short word and limited to the possibilities: White, Black, Asian, Mixed
    - Ethnicity (Hispanic or not)
    - Education

- Risk at Screening
  - Daily alcohol use
  - HSV-2 at screening
  - Circumcised
  - Age at entry
  - Analysis population indicators (ITT, mITT, PP, safety)
  - Other key variables
- b. Longitudinal HIV-1 visit data with one record per visit per patient and including at least the following fields:
- Patient ID
  - Treatment assignment
  - Date of first use of study drug
  - Date of current visit
  - Study day of current visit
  - Results of HIV test

All dates should be numeric or in SAS date formats.

- c. Important covariates selected for subgroup analyses, including at least adherence data (i.e., % of pill use in CO-US-104-0288). If the adherence data are collected on a different schedule from HIV tests, then also include a dataset with one record per date at which adherence were collected per patient and organized similarly to the dataset containing visit by visit date about HIV tests.
- d. The analysis datasets for CO-US-104-0380 should be changed according to the study design and efficacy findings.
8. Please clarify whether data for trial CO-US-104-0288 come from the file labeled 288 or from the file labeled 288\_addendum. The required datasets and all source input datasets used for the generation of the required datasets should be submitted to the CDER EDR. SAS programs for the generation of the new datasets should be provided.
9. Please clarify the relationship between the variables HIVSTAT, RESULTS1 and RESULTS2 in the dataset HIV for trial CO-US-104-0288. Please explain what 0 means as a value for these variables (e.g. not recorded).
10. Please provide any data on adherence to condoms by visit for both trials. If available, such data should include a variables measuring how many times condom protected sex occurred since the previous visit and how many times condom unprotected sex occurred since the previous visit.

### **Clinical Virology:**

11. Please submit a line-item virology dataset that consolidates pharmacokinetic and virologic data. Specifically, the file should allow for the comparison of drug concentrations, virus

titers, and genotypic data of samples collected at, or near, the same time point(s). We request that the file include the following data:

- Subject ID
- Trial (i.e., iPrEx or Partners PrEP)
- Cohort
- Time of seroconversion (Days from Baseline)
- HIV-1 subtype
- Time of PK Sample Collection (Days from Baseline)
- TFV concentration
- TFV-DP concentration
- FTC concentration
- FTC-TP concentration
- Time of virology sample collection (Days from Baseline)
- HIV-1 RNA load
- Genotypic data (complete HIV-1 RT amino acid sequence: if deep sequencing was used, provide a consensus amino acid sequence, identify variants that occurred in more than 1 individual and their percent within an individual's population); blank cells should be used for positions matching reference RT sequence (see guidance on submission of HIV-1 resistance data). Provide a separate dataset for allele-specific RT-PCR.
- Genotypic data of the Index Subject if resistance-associated substitutions are identified in the Partner Subject (if available from Partners PrEP). Include an identifier for matching with the appropriate partner and a column with “Y” or “N” as to whether a phylogenetic comparison of the index and partner viruses indicates that the partner was the probable source of the subject's infection.

Multiple rows may be included for the same subject if samples collected at multiple time points were evaluated. Also, please identify the assays used for RNA load determination and genotypic data analysis (e.g., allele-specific, ultra-deep, or population-based nucleotide sequencing assay).

12. Please provide study reports for the phenotypic and genotypic studies that were conducted for each trial, including detailed methodologies and a description of the performance parameters of assays that have not been approved. The assay descriptions should include primer and probe sequences (when applicable), a description of the sensitivity limits for minority populations, and—in the case of allele-specific RT-PCR—the detection limits for each of the degenerate bases within a codon for each resistance-associated substitution that was evaluated).
13. Please conduct an expanded HIV-1 resistance analysis for subjects who failed prophylaxis and had detectable drug levels or who were missing those pharmacokinetic data. The analysis should include a genotypic characterization of reverse transcriptase using an assay that is sensitive to minority species (e.g., 454 sequencing) and a phenotypic characterization for emtricitabine and tenofovir susceptibility if no known resistance-associated substitutions are identified.

## **Clinical Pharmacology**

14. Please submit all available method validation reports and bioanalytical study reports for both Phase 3 studies used in the analysis of tenofovir and emtricitabine concentrations in plasma and PBMCs.
15. If available, please provide the time of blood sampling (for analysis of plasma and PBMC drug concentrations) relative to the approximate time of the previous dose of study drug for all subjects (based on direct observation or self-reporting) from whom you collected samples in both Phase 3 studies. Please include this information as a separate data column in the DRUGORIG and DRUGLVL datasets. As an alternative, you may include this information in the consolidated PK and virology dataset(s) as described in the Clinical Virology request above.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE SCHUMANN  
01/20/2012

**From:** Schumann, Katherine  
**Sent:** Friday, January 20, 2012 2:10 PM  
**To:** 'Dara Wambach'  
**Cc:** Regulatory Archives  
**Subject:** NDA 21752 S-030 Truvada PrEP - Partners PrEP demographic dataset from 1/11/12

Dear Dara,

Thank you for your voice mail. As I mentioned over the phone, we have also identified errors in the Partners PrEP demographic dataset that was submitted on 1/11/12. Specifically, we noted the following:

We have found a significant discrepancy in the **subj038.xpt** dataset you submitted last week. There appear to be 107 subjects (PTID) in the ITT group who are listed twice, sometimes with conflicting treatment arm or clinic site assignments. Therefore, only 4544 subjects appear to be accounted for by this dataset. The **RANDARM.xpt** dataset submitted with the original sNDA has one unique subject ID per row, but includes 9516 subject IDs - both partner and index subjects - with no facile way of differentiating between the two populations. Please submit a corrected subject dataset that has the correct treatment arm and site assignments for enrolled partner subjects. In the meantime, please verify that the **RANDARM.xpt** file has the correct treatment arm assignments.

Thank you for proposing to submit a corrected dataset.

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
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KATHERINE SCHUMANN  
01/20/2012

# MEMORANDUM OF TELECON

DATE: January 6, 2012

APPLICATION NUMBER: NDA 21752 S-030

BETWEEN

**Gilead:** Andrew Cheng, MD, PhD, SVP HIV Therapeutics & Development Operations  
Michael Wulfsohn, VP, Biometrics  
Ramin Ebrahimi, Director, Biostatistics  
Sandy Chang, Director, Statistical Programming  
David Pizzuti, MD, VP, Regulatory Affairs  
Paul Tomkins, Senior Director Regulatory Affairs  
Dara Wambach, MA, Associate Director, Regulatory Affairs

AND

**DAVP:** Debra Birnkrant, M.D., Division Director  
Jeffrey Murray, M.D., M.P.H., Deputy Division Director  
Peter Miele, M.D., Clinical Reviewer  
Charu Mullick, M.D., Clinical Reviewer  
Karen Winestock, Chief, Project Management Staff  
Linda Onaga, M.P.H., Regulatory Project Manager  
Katherine Schumann, M.S., Regulatory Project Manager

**SUBJECT:** Issues regarding datasets submitted in Truvada PrEP supplement (S-030)

**BACKGROUND:** On December 14, 2011, Gilead submitted an efficacy supplement (NDA 21752 S-030) for a new indication for TRUVADA (emtricitabine/tenofovir disoproxil fumarate) for pre-exposure prophylaxis of HIV-1.

At the internal Filing/Planning meeting held on January 5, 2012, reviewers from the clinical virology, statistics and clinical disciplines identified significant problems with the datasets submitted by Gilead for the two pivotal trials included in the supplement. Statistics also recommended that DAVP request analysis datasets from the sponsor, although that was not considered a refuse to file issue.

A teleconference was held between the FDA and Gilead on January 6, 2012, to explain the issues identified by the reviewers during the filing meeting and ask Gilead how they could assist the Division to facilitate review of the data.

## DISCUSSION POINTS:

Dr. Birnkrant explained that the main issue for discussion is that reviewers from multiple

disciplines have found it difficult to navigate the datasets submitted to the NDA supplement. In addition, the Division would like to request analysis datasets for the two pivotal trials and additional information regarding the FEM-PrEP trial, which was not submitted to the sNDA.

Dr. Miele further explained that he would like Gilead to propose a way forward to resolve the issues identified with the raw datasets. Gilead responded that the raw datasets were all that were received from the respective study teams and that analysis datasets were not created by those groups. Gilead suggested that the reviewers look at the analysis guides appended to the Statistical Analysis Plan for each trial, as that is what Gilead used to do their own analysis of the iPrEX data. Dr. Birnkrant asked for the exact location of the analysis guides, and Gilead replied that they would send the guides as stand alone PDFs following the teleconference (post-tcon note: the PDFs were received via email on 1/6/2012).

Gilead explained that they had a CRO work on the analysis for iPrEX and that they could request and submit the analysis datasets. Gilead estimated needed one week to make the analysis datasets “submission ready.”

Dr. Murray then asked if the CRO might be able to perform a similar analysis of the Partners PrEP data, at least for key safety parameters, such as renal outcomes. Gilead replied that they would need to speak to the Partners PrEP study team before fully committing, but that they estimated a timeframe of 3-4 weeks to prepare analysis datasets for the trial. Gilead agreed to speak to the Partners PrEP study team and update the Division after the discussion.

Gilead agreed that they would like to hear additional, specific examples of problems that the reviewers had encountered with the datasets. Dr. Miele explained that the data elements are not well defined in the define pdf document. Gilead responded that the definitions could be traced back to the annotated CRFs. Dr. Miele responded that it is extremely time-consuming to refer back to the annotated CRFs to understand each field in each of the datasets given the volume of datasets submitted. Gilead agreed to take the issue off-line to determine how it could best be resolved, and possibly schedule a follow-up teleconference with the Division to discuss the problem further.

Dr. Miele also asked for clarification regarding the iPrEX safety analyses, specifically, whether they addressed the cumulative dataset or only data prior to the May 1 cutoff. Gilead explained that the summary was based primarily on the May 1 cutoff.

Additional examples of dataset issues provided by Dr. Miele included the following:

1. In the AE datasets, multiple MedDRA terms are present in a single field that need to be in separate fields to permit analysis.
2. The treatment arms for each participant should be flagged in the various datasets.
3. A “change from baseline” variable should be available for the lab datasets.

Gilead agreed that all of the issues could be fixed and explained they are willing to continue to revise the datasets if additional problems arise during the review cycle. DAVP offered to send a correspondence containing a longer list of specific issues, to which Gilead responded that such a list would be helpful.

Dr. Birnkrant reminded Gilead that the Division would like to see additional data from the FEM-PrEP trial, specifically the correlation of drug concentrations to efficacy. Gilead agreed to speak to FHI and then get back to the Division regarding this request.

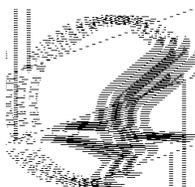
**ACTION ITEMS:**

1. Gilead will prepare and submit the analysis datasets for the iPrEX trial. The estimated preparation time required is one week.
2. Gilead will speak to the [REDACTED] <sup>(b) (4)</sup> to determine the feasibility and estimated timeline for providing the Partners PrEP analysis datasets to DAVP.
3. Gilead will speak to FHI regarding the feasibility of providing data from the FEM-PrEP trial.
4. DAVP will provide Gilead with a list of specific issues with the datasets from each review discipline to assist them in the preparation of the revised datasets.
5. An additional teleconference will be scheduled for further discussion of specific dataset issues.

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KATHERINE SCHUMANN  
01/19/2012



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Silver Spring, MD 20903

**MEMORANDUM OF ELECTRONIC CORRESPONDENCE**

**NDA:** 21752 S-30

**Drug:** Truvada (emtricitabine/tenofovir disoproxil fumarate)

**Date:** January 4, 2012

**To:** Dara Wambach, M.A., Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc.

**From:** Katherine Schumann, M.S., Regulatory Project Manager, DAVP

**Subject:** NDA 21752 S-30 Truvada PrEP - Request for Information

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Please refer to your New Drug Application (NDA) 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/tenofovir disoproxil fumarate).

In our preliminary assessment of your submission package, we have identified the following issue that may impede the conduct of a substantive and timely review. This issue warrants immediate attention as inspection of foreign sites needs to be initiated early within the current review timeline. Please submit your response to our request by January 11, 2012.

1. Please provide a dataset for each study (CO-US-104-0288 and CO-US-104-0380) that lists by clinical site and treatment arm: the number of participants screened, enrolled, and discontinued; the number of seroconversions per participants enrolled per site (or site specific efficacy effect size and variance); and the number of AEs, SAEs, deaths, and protocol violations. In addition, include the full contact information for each investigator/clinical site.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

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Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research

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KATHERINE SCHUMANN  
01/04/2012



NDA 21752/S-030

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

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

Dear Ms. Wambach:

We have received your December 14, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 21752  
**SUPPLEMENT NUMBER:** 030  
**PRODUCT NAME:** TRUVADA (emtricitabine/tenofovir disoproxil fumarate)  
Tablets, 200 mg and 300 mg  
**DATE OF SUBMISSION:** December 14, 2011  
**DATE OF RECEIPT:** December 15, 2011

This supplemental application proposes the following change: a new indication for the use of TRUVADA (emtricitabine/tenofovir disoproxil fumarate) tablets, pre-exposure prophylaxis of HIV-1 infection (PrEP).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 13, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

## **FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Katherine Schumann, M.S.  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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KATHERINE SCHUMANN  
12/22/2011