CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of Final Amendments to the Risk Evaluation and Mitigation Strategy (REMS) Proposed for TRUVADA for a Pre-Exposure Prophylaxis Indication

Date:	July 13, 2012
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M. D., F.A.A.P., Senior Medical Officer, Division of Risk Management (DRISK) Ana Tavakoli, M.A., Health Communications Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)
Therapeutic Class:	Nucleoside/Nucleotide (*emtricitabine/tenofovir disoproxil fumarate)* Analog HIV-1 Reverse Transcriptase Inhibitor
Dosage and Route:	Fixed-dose combination Tablet, 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate
Application Type/Number:	NDA 021-752 Supplement 30
Subject:	Review of the Proposed REMS for TRUVADA for a Pre-Exposure Prophylaxis (PrEP) Indication
Applicant/sponsor:	Gilead Sciences, Inc. (Gilead)
OSE RCM #:	2012-73

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates the proposed Risk Evaluation and Mitigation Strategy (REMS) for Truvada for a pre-exposure prophylaxis (PrEP) indication to reduce the risk of sexually transmitted HIV-1. Among the adverse events of special interest associated with use of Truvada for PrEP and the development of drug resistance in persons who seroconvert to HIV-1 positive while continuing to take Truvada for PrEP, it was determined that a REMS will be required to ensure that the benefits outweigh the risks. The proposed REMS was submitted on December 15, 2011 and amended on May 8, 2012; June 5, 14 and 19, 2012; and July 3, 5 and 12, 2012.

The requirement for and elements of the REMS was discussed at numerous internal meetings including at a Regulatory Briefing on June 10, 2011, discussion at the REMS Oversight Committee (ROC) meeting on March 2, 2012, and at Center Director Briefings on July 14, 2011 and May 16, 2012. FDA also obtained external feedback regarding the risk management and REMS for PrEP at a Forum for Collaborative HIV Research on August 19, 2011 and at the Antiviral Drugs Advisory Committee meeting on May 10, 2012.

The goals of the REMS for TRUVADA for a 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

The REMS for Truvada for PrEP is comprised of a Medication Guide, an Element to Assure Safe Use, specifically Prescriber Training and Education that is not linked to drug distribution, and a Timetable for Submission of Assessments to be submitted annually.

Based upon Agency comments, the applicant incorporated final revisions to the REMS Document, appended REMS prescriber training and educational materials, and the REMS website. [1, 2, 3] The proposed REMS Assessment Plan incorporates the additional the components included in the advice letter (dated June 26, 2012) and is acceptable to the DRISK.

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[1] See DRISK review, "Interim Comments to the REMS Proposed for Truvada for a PrEP Indication, Set 1 (dated April 12, 2012) written by Carolyn L. Yancey, M. D, F.A.A.P., DRISK

[2] See DRISK review, "Interim Comments to the Amendments to the REMS Proposed for Truvada for a PrEP Indication, Set 2" (dated May 29, 2012) written by Carolyn L. Yancey, M.D., F.A.A.P., DRISK

[3] See DRISK review, "Interim Comments on Amendments to the REMS Proposed for TRUVADA for a PrEP Indication (Set 3) (dated June 25, 2012) written by Carolyn L. Yancey, M.D., F.A.A.P., DRISK

DRISK finds the proposed REMS for Truvada for PrEP acceptable as submitted on July 12, 2012. The REMS should be approved.

1 INTRODUCTION

This is a review of the proposed Risk Evaluation and Mitigation Strategy (REMS) for Truvada for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually transmitted HIV-1.

1.1 BACKGROUND

Over the past decade, the incidence of new HIV infections in the United States has remained stable, despite widespread knowledge of HIV/AIDS and decades of intensive condom promotion. The U.S. Centers for Disease Control (CDC) estimates that approximately 50,000 persons are infected annually with HIV in the United States.[4] Moreover, the HIV epidemic is disproportionally affecting men who have sex with men (MSM) and men and women of color; in some populations, such as young African-American MSM, the rates of new HIV infections have dramatically increased in recent years.

To combat these trends, for the first time in U.S. history, a national strategy has been developed to address the domestic HIV epidemic. The primary objective of the National HIV/AIDS Strategy is to lower the annual number of new infections by 25% in 5 years.[5] As noted in the strategy, a multipronged approach to HIV prevention is needed, including the combination of condom promotion, risk reduction counseling, treatment of sexually transmitted infections, and increased uptake and retention of HIV-infected individuals in healthcare. However, given the limited effectiveness of current prevention methods and the lack of an available vaccine, there remains an unmet medical need to identify and implement new evidence-based approaches to HIV prevention that can augment existing strategies.

The use of approved antiretroviral drugs in high risk, HIV-uninfected individuals as pre-exposure prophylaxis (PrEP) against HIV infection offers a potential intervention for primary HIV prevention. PrEP is part of an overall prevention strategy that could potentially contribute to addressing this unmet need.

The PrEP clinical trials utilize the drug tenofovir or a tenofovir/emtricitabine combination (Truvada) that is an oral tablet. Emtricitabine (EMTRIVA/FTC) is a synthetic nucleoside analog of cytidine. Tenofovir disoproxil fumarate (tenofovir DF/TDF) is converted *in vivo* to tenofovir, an acyclic nucleoside phosphate (nucleotide) analog of adenosine 5'-mono-phosphate. Emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase. Truvada is a fixed-dose combination tablet containing emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg). Truvada, approved on August 2, 2004 for the treatment of HIV-1 infection in adults over 18 years

[4] Prejean J et al. Estimated HIV incidence in the United States, 2006–2009. PLoS ONE 6(8): e17502.

[5] Office of National AIDS Policy. National HIV/AIDS Strategy. Washington, DC: Office of National AIDS Policy; 2010. http://www.whitehouse.gov/administration/eop/onap/nhas. Accessed: March 19, 2012.

of age, in combination with other antiretroviral products, remains one of the most extensively prescribed products for treatment of established HIV-1 infection.[6]

1.2 REGULATORY HISTORY

Gilead submitted the supplemental application on December 15, 2011 for the use of Truvada for pre-exposure prophylaxis of HIV-1 infection (PrEP), dosed once daily.

The applicant was advised to submit a proposed REMS with the supplemental application for the PrEP indication because the risk of developing drug resistance in the setting of ongoing Truvada use following HIV infection is considered serious. Development of drug resistant HIV-1 variants may limit treatment options for an individual who has sero-converted while taking Truvada for PrEP and may increase the risk of transmitting resistant virus to others.

The elements of the REMS were discussed and consensus was reached at numerous internal meetings including at a Regulatory Briefing on June 10, 2011, REMS Oversight Committee (ROC) meeting on March 2, 2012, and at Center Director Briefings on July 14, 2011 and May 16, 2012. FDA also obtained external feedback regarding the risk management and REMS for PrEP at a Forum for Collaborative HIV Research on August 19, 2011 and at the Antiviral Drugs Advisory Committee meeting on May 10, 2012.

There was consensus within the Center for Drug Evaluation and Research (CDER) that drug access should not be restricted to only trained prescribers or to individuals with documentation of safe use conditions. The documentation of safe use conditions, such as a negative HIV-1 test result, prior to receiving Truvada for a PrEP indication is not being required as it will likely restrict patient access for patients being treated for established HIV infection and negatively impact adherence for individuals taking Truvada for a PrEP indication. We also heard stakeholder feedback against required lab monitoring (a HIV-1 negative test result) to fill a prescription for Truvada for PrEP. As stated in the Executive Summary, consensus is that the REMS for Truvada for a PrEP Indication is comprised of a Medication Guide, an Element to Assure Safe Use, as Prescriber Training and Education that is not linked to drug distribution, and a Timetable for Submission of Assessments to be submitted annually.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following comments and teleconferences were held with the applicant since the last DRISK review in regards to the proposed REMS, postmarketing studies, and prescribing information:

- June 14, 2012: The Agency held a teleconference with the applicant to discuss the postmarketing requirements (PMRs) and postmarketing commitments (PMCs) including clarifications about appended REMS training and educational materials in a PMC (proposed Observational Study)

[6] Department of Health and Human Services Adult and Adolescent HIV Treatment Guidelines, Revised March 2012

- June 26, 2012: The Agency sent comments to the applicant about revisions to the REMS Document (minor grammatical revisions) and appended REMS training and educational materials including the REMS website landing screenshot. The Agency also sent revised labeling to the applicant.
- June 27 and 28, 2012: The Agency sent comments to the applicant about additional minor edits in the REMS Document and specific appended REMS materials
- July 6, 2012: The Agency sent final revisions (in track changes) to the applicant in the REMS Document and all appended REMS training and educational materials including the REMS website. The applicant must accept all revisions to the REMS Document and the appended materials including the REMS website for the REMS to be acceptable to the Agency.

The following materials were submitted for review for Truvada for PrEP (Supplement 30) with regards to the proposed REMS, postmarketing studies, and prescribing information:

- Proposed REMS, submitted December 15, 2011 (sequence number/seq no. 734)
  - REMS Amendment submitted May 8, 2012 (seq no. 740)
  - REMS Amendment submitted June 5, 2012 (seq no. 745)
  - REMS Amendment submitted June 14, 2012 (seq no. 748)
  - REMS correspondence submitted June 19, 2012 (seq no. 749)
  - REMS Amendment submitted July 3, 2012 (seq no. 755)
  - REMS Amendment submitted July 5, 2012 (seq no. 756)
  - REMS Amendment submitted July 12, 2012 (seq no. 763)
- Prescribing Information:
  - Revised labeling submitted May 22, 2012 (seq no. 742)
  - Revised labeling submitted June 8, 2012 (seq no. 747)
  - Revised labeling submitted June 21, 2012 (seq no. 750)
  - Courtesy copy of revised labeling sent June 29, 2012 (in response to the Agency's revisions sent June 26, 2012)
  - Revised labeling submitted July 2, 2012 (seq no. 754)
  - Final labeling submitted July 11, 2012 (seq no. 760)
- Postmarketing Studies:
  - PMR/PMC general correspondence submitted June 29, 2012 (seq no. 753)
  - PMR/PMC general correspondence submitted July 6, 2012 (seq no. 758)
  - PMR/PMC response to information request submitted July 9, 2012 (seq no. 759)

2.2 ANALYSIS TECHNIQUES

The proposed REMS for Truvada for PrEP was reviewed for conformance with the Agency's comments sent to the applicant on the REMS Document and appended REMS materials.

3 RESULTS OF REVIEW OF THE PROPOSED RISK EVALUATION AND MITIGATION STRATEGY FOR TRUVADA FOR PRE-EXPOSURE PROPHYLAXIS

3.1 OVERVIEW OF CLINICAL PROGRAM

The efficacy supplement, sNDA 021-752/Supplement 30, in support of Truvada for PrEP includes two adult populations, men who have sex with men (MSM) and heterosexual discordant couples. Two pivotal Phase 3 clinical trials and one supportive Phase 2b clinical trial support Truvada proposed for PrEP:

- CO-US-104-0288, iPrEx Trial: "Chemoprophylaxis for HIV Prevention in Men" also known as Pre-Exposure Prophylaxis Initiative to compare FTC/TDF to Placebo (PBO) Treatment: Daily oral FTC/TDF compared to PBO
- CO-US-104-0380, Partners PrEP Trial: Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples" compared to PBO. Treatment: Daily oral TDF or FTC/TDF
- CDC 4323 US Trial: from the Centers for Disease Control (CDC), "CDC 4323 U. S. trial in Men Who Have Sex with Men." assessed safety, adherence, and acceptability of PrEP in subjects taking once-daily TDF or PBO

The iPrEX and Partners PrEP trials were designed as randomized (R), prospective, PBO-controlled (PBO-C) trials including monthly HIV-1 testing, risk-reduction counseling, free condoms, and treatment of symptomatic sexually transmitted infections (STIs) provided at monthly visits per protocol.

Efficacy

The iPrEx and Partners PrEP trials form the basis for TDF/FTC efficacy analyses. The primary outcome measure was the incidence of documented HIV seroconversion (the percent of risk reduction of HIV-1 infection) in both trials powered to show at least 30% risk reduction. Once-daily Truvada demonstrated a statistically significant reduction in the risk of acquisition of HIV-1 infection compared with PBO in the two Phase 3 trials. The CDC 4323 US trial demonstrated supportive efficacy though the trial design was to evaluate clinical safety. An effective concentration threshold for TDF prophylaxis for HIV-1 infection could not be determined in this clinical development program.

3.2 SAFETY

Clinical safety based on the known safety profile of FTC and TDF alone, or in combination, is derived from more than 4 million patient-years in clinical studies and postmarketing settings in patients with HIV infection.[7] In addition, clinical safety is based on exposure in iPrEx, Partners PrEP, and CDC 4323 US trials. Clinical exposure, by trial, follows:

[7] NDA 021-752, Supplement 30, Module 2.5, Clinical Overview, Section 5 Overview of Safety, page 40 of 63.

- iPrEx: Randomized 2,499 subjects; subjects were followed for a median of 71 weeks (1251 received Truvada and 1248 received PBO).
- Partners PrEP: Randomized 4,758 subjects; subjects were followed for a median of 87 weeks
- CDC 4324 US: Randomized 400 subjects in a Behavioral Analysis Cohort; 373 dispensed study drug; 323 completed all study visits through 24 months.

No new adverse reactions to Truvada for PrEP were observed in the two R, PBO-C clinical trials (iPrEX and Partners PrEP) in which HIV uninfected adults received Truvada for PrEP. The most common side effects reported in greater than or equal to 2% of subjects with Truvada for PrEP include System Organ Class Gastrointestinal Disorders (diarrhea, nausea, abdominal pain), Nervous System Disorders (headache), and in Investigations (weight decreased). The known major safety risks associated with Truvada (renal, bone, and hepatic flares in the setting of hepatitis B infection) were infrequent in these trials.

3.2.1 Drug Resistance

The potential development of drug resistant variants in individuals who seroconvert while taking TRUVADA for PrEP is the primary safety concern with use of Truvada for PrEP of sexually acquired HIV-1 infection. Development of drug resistant HIV-1 variants may limit treatment options for an individual who has seroconverted while taking Truvada for PrEP and may increase the risk of transmitting resistant virus to others.

Both pivotal trials include reports of seroconversion though the numbers are small for specific virus substitutions. Brief summary follows:

iPrEX

No amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the Truvada group and 83 subjects in the PBO group who became infected with HIV-1 during the clinical trial. Ten (10) subjects were observed to be HIV-1 infected at the time of trial enrollment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 or 2 in the Truvada group and 1 of 8 in the PBO group). One of the two subjects in the Truvada group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment.

Partners PrEP

No variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the Truvada group, 15 subjects in the Viread group, and 51 subjects in the PBO group. Fourteen (14) subjects were observed to be HIV-1 infected at enrollment (5 in Truvada group, 3 in the Viread group, and 6 in the PBO group).

- One (1) of three (3) subjects in the Truvada group (who was infected with wild type virus at enrollment) selected an M184V expressing virus by week 12.
- Two (2) of 5 subjects in the VIREAD group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrollment developed a K65R substitutions by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions at seroconversion at week 60. Although, baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted.

Following enrollment, 4 subjects (2 in the VIREAD group, 1 in the TRUVADA group, and 1 in the PBO group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to NNRTIs but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.

3.3 PROPOSED REMS GOALS

The final agreed upon goals of the REMS for TRUVADA for a 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

3.4 PROPOSED REMS ELEMENTS

The REMS for Truvada for PrEP is comprised of a Medication Guide, an Element to Assure Safe Use, specifically Prescriber Training and Education, and a Timetable for Submission of Assessments..

Comment:

The final formatted REMS for TRUVADA for a PrEP Indication (submitted on July 12, 2012) is presented in the **Attachments** to this review. The applicant accepted all of the revisions (in track changes) as stipulated by the Agency.

3.4.1 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.

Comment:

The Medication Guide includes revisions as stipulated in the Patient Labeling Review (dated June 20, 2012) and in comments from the DAVP based on labeling revisions.

3.4.2 Element to Assure Safe Use

The applicant will ensure that training and education materials will be available for completion by healthcare providers who prescribe TRUVADA for PrEP via the TRUVADA for a PrEP Indication Healthcare Professional Education Program. The Training and Education will be targeted to primary care physicians, including internal medicine, family practice, and general medicine physicians, Infectious Diseases specialists, Obstetrician-gynecologists, and Addiction specialists. The Agency concluded that a robust educational program was required for the intended prescriber population, since they may be generalists, not familiar with HIV or drugs used to treat HIV-1 infection, and/or with parameters that make patients at high risk of acquiring HIV.

The program comprises the following:

- Prescriber Educational Slide Deck
- Training Guide for Healthcare Providers
- Important Safety Information about TRUVADA for a PrEP Indication for Healthcare Providers
- Important Safety Information about TRUVADA for a PrEP Indication for Uninfected Individuals
- 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
- Safety Information Fact Sheet to be included in professional society journals on a quarterly basis for 3 years
- REMS Website for TRUVADA for a PrEP Indication
- Checklist for Prescribers to manage an individual considering or taking TRUVADA for a PrEP indication

The Checklist for Prescribers and the Agreement Form were added to the REMS in response to the Antiviral Drugs Advisory Committee's recommendation to strengthen prescriber training and educational materials.

Comments:
The training and education program for healthcare providers will not be linked to drug distribution but Gilead will ensure that the materials are available to all healthcare providers likely to prescribe Truvada for PrEP. Drug access would not be restricted to only trained prescribers because such a restriction would likely impede patient access for patients being treated for established HIV infection and negatively impact adherence for individuals taking Truvada for a PrEP indication. The Agency concurred that a different trade name and/or packaging would not prevent circumventing a restricted REMS program.

3.4.3 Proposed Timetable for Submission of Assessments

The timetable for submission of assessments is annually from the date of approval of the REMS.

Comment:

A 6-month assessment is not being required because the sponsor expressed concern with meeting the proposed timetable with results from comprehension testing of all REMS materials; this includes allowing time for submission and review of protocols and for sufficient time to conduct comprehension testing. In addition, recent feedback from the Food and Drug Administration (FDA) Social Science Workshop held by the Agency on June 7, 2012 included the necessity of pretesting REMS materials and concerns about timelines with time to recruit.[8]

3.5 NON-REMS STRATEGIES

The following strategies proposed under the communication plan in the applicant's original REMS submission:

- Option for prescribers to register and obtain access to the following:
  - Educational materials for clinic settings
  - Vouchers for free condoms for individuals at high risk
  - Vouchers to provide subsidized HIV-1 testing to appropriate individuals
  - Assistance in providing subsidized HIV-1 viral resistance testing to individuals who seroconvert
- Resources and materials for individuals at high risk for acquiring HIV-1 who are taking Truvada prophylaxis, including the following:
  - Opt-in reminder service to obtain regular testing for HIV-1 and other STDs
  - Vouchers to obtain free condoms

While the Agency believes that these measures will help support a comprehensive HIV prevention strategy, these materials are not typical tools that are enforceable under an approved REMS. In a May 17, 2012 teleconference with the applicant, the Agency reiterated that these strategies can be executed outside of the required REMS program.

3.6 PROPOSED REMS ASSESSMENT PLAN

The proposed REMS assessment plan includes the following:

1. An evaluation of uninfected individuals' understanding of the serious risks of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) Tablets
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
3. Number of prescribers who completed the training and educational program via the Gilead website or through mailings
4. Demographics of prescribers and uninfected individuals
5. Prescribers, by specialty type, who prescribe Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for PrEP, to the extent possible

[8] REMS Assessments: Social Science Methodologies to Assess Goals, FDA Public Workshop, www fda.gov/Drugs/NewsEvents/ucm132703.htm

6. Estimates of the total number of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets prescriptions for a PrEP indication via third party vendor(s)
7. Drug resistance in negative HIV-1 individuals who seroconvert to positive HIV-1 during use of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets as monotherapy, to the extent possible
8. Compliance with regular HIV-1 testing (at least every 3 months) in individuals using Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for PrEP, to the extent possible
9. Comprehension testing of the REMS training and educational materials, including the Medication Guide, will be included in the 12-month assessment
10. Information received from adverse event reporting from spontaneous sources, published literature, regulatory agencies, clinical studies and trials (clinical serious adverse events/SAEs) and solicited sources for entry into the Gilead drug safety database
11. Gilead will engage a third party vendor to complete the following:
    a. Conduct a web-based phone and paper-based option, self-administered Knowledge, Attitude and Behavior (KAB) survey for prescribers and uninfected individuals taking (or recently taken) Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for a PrEP indication. Surveys will assess prescriber and uninfected individuals understanding of the risks associated with use of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for a PrEP indication, their understanding of the importance of compliance, and risk behavior to assess the effectiveness of the REMS outreach and education.
    b. Gilead will develop and administer these surveys anonymously on a periodic basis to a random sample of uninfected individuals at high risk for acquiring HIV-1 infection currently taking (or who have taken) Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for a PrEP indication and of prescribers who have registered to take the survey.
12. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
13. Information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, Gilead must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, Gilead must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. Gilead can

satisfy these requirements in the REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Comments:

The REMS assessment plan does not include reporting on compliance with treatment, HIV-1 testing, risk behavior associated with obtained reports of lack of efficacy, or updates on the Gilead PrEP registry in the proposed observational study (See **Section 3.7 Postmarketing Studies**, in this review). The Agency accepts that these reports and data will be included in the demonstration projects and/or the observational study.

As presented at the Antiviral Drugs Advisory Committee meeting, there are a number of challenges in assessing whether or not the REMS will be effective. It will be challenging to capture and report prescriber and individual usage data for Truvada for PrEP. There is no specific International Statistical Classification of Disease and Related Health Problems (ICD-9) Code to identify an uninfected individual taking Truvada for PrEP. Truvada is currently approved for use in combination with at least one other antiretroviral medication for treatment of established HIV-1 infection, so use of Truvada when prescribed without other concomitant antiretroviral drugs may give some indication of the extent of Truvada use for PrEP. For the same reasons, it will be challenging to measure the proportion of prescribers of Truvada for PrEP who have undergone the REMS training and education program.

Finally, it will be difficult to determine whether the REMS has had an impact in reducing the risk of development of resistant HIV-1 variants because the proposed REMS does not include documentation of safe use with required monitoring of a negative HIV-1 test result to fill a prescription for Truvada for PrEP. The proposed REMS does not include a registry of uninfected individuals prescribed Truvada for PrEP or documentation of safe use, such as a negative HIV-1 test result.

3.7 PROPOSED POSTMARKETING STUDIES

The approval of Truvada for PrEP will include one PMR and four PMCs. Brief summary descriptions to be included in the approval letter follow:

- PMR 1: A Drug Resistance Study will collect data from individuals participating in demonstration projects who seroconvert during follow-up. Data will be collected over a time-period not to exceed 3 years and will be completed when data are collected from 150 seroconverters enrolled in demonstration projects. See sNDA 021-752 for a list of the required data to be collected.
- PMC 2: A "Prospective Study of Women Taking Truvada for PrEP during Their Pregnancy" will follow 200 women who become pregnant while taking Truvada for PrEP and continue Truvada during their pregnancy. Data will be collected on pregnancy outcomes that should include but not be limited to:
    a. HIV seroconversion in mothers and infants
    b. Spontaneous and elective abortions

c. Pre-term deliveries and infant outcomes including the presence or absence of congential malformations

- PMC 3: A Drug Utilization Study will provide comprehensive national drug utilization data in sufficient detail to characterize use of Truvada for PrEP and individuals taking Truvada for PrEP. These data will be submitted to FDA every 6 months for 3 years, for both generic (as applicable) and brand name products containing FTC/TDF, starting one-year following approval of Truvada for a PrEP indication.
- PMC 4: An analysis of data from ongoing and planned demonstration projects of Truvada 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. 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 performed every three months.
- PMC 5: Utilize a survey on individual knowledge, attitudes, and behaviors and evaluate the association/prediction with future adherence to once-daily Truvada for pre-exposure prophylaxis. The effect of adherence will be put into the context of sexual and non-sexual individual behaviors that may affect the risk of HIV infection. The survey will be implemented in a national demographically balanced sample.

See the Approval letter from the DAVP for additional details and the timetable for the PMR and each PMC.

4 DISCUSSION

The approval of Truvada for PrEP to reduce the risk of sexually transmitted HIV-1 carries the risk of drug resistant HIV-1 variants in persons who continue to take Truvada following HIV seroconversion. In order to reduce the risk of acquiring HIV-1 drug resistance, Truvada for PrEP must only be used as part of a comprehensive prevention strategy. This strategy includes:

- Safer sex practices that include consistent and correct use of condoms
- Risk reduction counseling
- Knowledge of their HIV-1 status and that of their partner(s)
- Prior to prescribing Truvada, confirmation a negative HIV-1 status using a highly sensitive diagnostic test capable of detecting viral ribonucleic acid (RNA) or p24 antigen
- While using Truvada for PrEP, HIV-1 testing should be repeated at least every 3 months using a highly sensitive diagnostic test (as above)
- Regular testing for other sexually transmitted infections (STIs) such as syphilis and gonorrhea

- Individuals must be regularly evaluated for current or recent signs and symptoms consistent with acute viral infections (e.g., fever , fatigue, myalgia, skin rash)

Each of these measures, in combination, is key because HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who continue to take only Truvada.

Because of the potential risk of drug resistance, FDA required a REMS for this indication to ensure that the benefits of the drug outweigh the risks. The importance of a comprehensive management approach for taking Truvada for a PrEP indication is included in the REMS goals, Medication Guide, prescriber training and educational materials, and in educational material directed toward uninfected individuals.

The Agency considered requiring prescriber training as a requirement for prescribing the drug and mandatory documentation of HIV testing in order to dispense the drug but determined that such restrictions would likely restrict access for patients with established HIV-1 infection who are being treated with Truvada and negatively impact adherence for uninfected individuals taking Truvada for PrEP. We also heard stakeholder feedback against restricting access to Truvada for PrEP by linking filling a prescription to documentation of a negative HIV-1 test result.

FDA believes that the educational efforts in the proposed REMS are sufficient to support the recommended REMS program. However, as discussed above (Section 3.6 Proposed REMS Assessment Plan), there are a number of challenges in assessing whether or not the REMS is effective. FDA considers the non-REMS strategies supportive and valuable. These strategies can be executed outside of the required REMS program.

The proposed REMS for Truvada for a PrEP Indication, (submitted on July 12, 2012) and all required revisions are based upon Agency comments. The DRISK Review Team finds the proposed REMS for Truvada for a PrEP Indication, to be acceptable.

The proposed postmarketing studies (described in **Section 3.7**) aim to assist in providing data that may not be discerned from the REMS assessments.

5 CONCLUSION

In conclusion, the amended proposed REMS for Truvada (emtricitabine/tenofovir disoproxil fumarate) for a PrEP Indication submitted on July 12, 2012 contains the agreed upon revisions to the REMS Document, appended REMS prescriber training and educational materials, and the REMS website. [1, 2, 3] The proposed REMS Assessment Plan incorporates the additional components included in the Advice letter (dated June 26, 2012) and is acceptable to the DRISK.

6 RECOMMENDATIONS TO THE DIVISION OF ANTIVIRAL PRODUCTS

We recommend approval of the REMS for Truvada for a PrEP indication. The DRISK requests that the REMS assessment plan be included in the approval letter.

ATTACHMENTS

Only the final appended REMS materials in WORD version are attached to this review. The other final REMS appended training and educational materials including the REMS website are in PDF format with the DAVP.

Initial REMS Approval: xx/xx/2012

Supplemental NDA 21-752

TRUVADA® (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)

7 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

8 II. REMS ELEMENTS

8.1 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.

8.2 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 providers who prescribe TRUVADA for a PrEP indication.

    a. Gilead will ensure that training and education materials will be available for completion by healthcare providers 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) 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 providers 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 providers 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 providers 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 piece is appended and part of the REMS

e. Gilead will ensure that, as part of training and education, the following materials are available to healthcare providers:

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) on the date of the first mailing.

Gilead will distribute the DHCP letter to the targeted healthcare providers 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 the 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 test results including a negative HIV-1 test result, sexually transmitted infections, signs and symptoms of acute HIV infection and hepatitis B, 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 Providers
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. This information will remain on the website for a period of 3 years from product approval.

8.3 C. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Gilead Sciences, Inc. will submit REMS Assessments to FDA annually 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.

IMPORTANT DRUG WARNING

Subject: FDA-Required Risk Evaluation Mitigation Strategy (REMS) for a new indication for TRUVADA® [TRUVADA for a pre-exposure prophylaxis (PrEP) indication]

A negative HIV-1 test must be confirmed immediately before starting TRUVADA for a PrEP indication. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for a PrEP indication following undetected HIV-1 infection.

Dear Healthcare Provider:

Gilead Sciences, Inc., would like to inform you of a new indication for TRUVADA (a fixed-dose combination of emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg), approved by the FDA on XXXXXXX, for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

The FDA has determined that a Risk Evaluation Mitigation Strategy (REMS) is necessary to ensure that the benefits of TRUVADA for a PrEP indication outweigh its risks.

The goals of the REMS for TRUVADA for a PrEP indication are:

1. To inform and educate prescribers, other healthcare providers (HCPs), and uninfected 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 a part of a comprehensive prevention strategy in order to reduce the risk of HIV-1 infection and that other preventive measures should also be used.

Before initiating TRUVADA for a PrEP indication

You MUST obtain a negative HIV-1 status immediately before prescribing TRUVADA for a PrEP indication in an uninfected individual. Drug-resistant HIV-1 variants have been identified with use of TRUVADA for a PrEP indication following undetected HIV-1 infection.

Do NOT prescribe TRUVADA for a PrEP indication to patients with HIV-1 infection or to individuals with signs or symptoms consistent with acute HIV-1 infection, such as

fatigue, fever, sweating, pain, rash, diarrhea or coughing fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).

Prescriber Action

You should review and discuss the content of the **Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis of Sexually Acquired HIV-1 Infection** with an uninfected individual considering or taking TRUVADA for a PrEP indication and refer to the **Checklist for Prescribers** regarding the management of an uninfected individual taking TRUVADA for a PrEP indication. (*Access **Agreement Form** and **Checklist** via www.truvadapreprems.com*)

The most important information you should know about prescribing TRUVADA for a PrEP indication to reduce the risk of acquiring HIV-1 infection is:

TRUVADA for a PrEP indication should only be used as part of a comprehensive prevention strategy including consistent and correct use of condoms and risk reduction counseling

All uninfected individuals at high risk for acquiring HIV-1 should only take TRUVADA for a PrEP indication after HIV-1 negative status is confirmed, to reduce the risk of development of resistant HIV-1 variants

All uninfected individuals at high risk must strictly adhere to the recommended TRUVADA daily oral regimen

Management of Uninfected Individuals

Uninfected individuals at high risk should:

- Be counseled about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission.
- Be tested to confirm that they are HIV-1 negative immediately before starting TRUVADA for a PrEP indication.
- Be tested for acute HIV-1 infection and checked for any signs or symptoms consistent with acute HIV-1 infection, such as fatigue, sweating a lot (especially at night), rash, vomiting, diarrhea, joint or muscle aches, headache, sore throat, or enlarged lymph nodes in their neck or groin.
- Be screened at least every 3 months for HIV-1 as determined by their prescriber to confirm that they are HIV-1-negative while taking TRUVADA for a PrEP indication to reduce the risk of acquiring HIV-1.

- Have their creatinine clearance calculated prior to initiating TRUVADA, and not receive TRUVADA for a PrEP indication if creatinine clearance is <60 mL/min. If a decrease in creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, the prescriber should evaluate potential causes and potential risks and benefits of continued use.

- Be tested for the presence of hepatitis B virus (HBV) before starting on TRUVADA for a PrEP indication. Severe acute exacerbations of hepatitis B have been reported in individuals who are co-infected with HBV and HIV-1 and have discontinued TRUVADA. Uninfected individuals taking TRUVADA for a PrEP indication who are infected with HBV need close medical follow-up for several months to monitor for exacerbations of hepatitis B in the event TRUVADA is discontinued. HBV-uninfected individuals should be offered vaccination.
- Be informed about the risk of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, which have been reported. TRUVADA should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness)
- Be informed that TRUVADA has only been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

REMS Website *(www.truvadapreprems.com)*

The REMS website provides access to the following:

- Specific information regarding the risks of TRUVADA for a PrEP indication

- Training and educational materials for prescribers that include safety information for uninfected individuals considering or taking TRUVADA for a PrEP indication, including the **Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis of Sexually Acquired HIV-1 Infection** and **Checklist for Prescribers**.

Reporting Adverse Events

To report any adverse events, suspected to be associated with the use of TRUVADA for a PrEP indication, contact:

- Gilead Pharmaceuticals, Inc at 1-800-445-3235 and/or
- FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), or online (https://www.accessdata.fda.gov/scripts/medwatch/)

This letter is not intended as a comprehensive description of the risks associated with the use of TRUVADA for a PrEP indication. Please read the enclosed Full Prescribing Information and Medication Guide for a complete description of safety risks.

Sincerely,
XXXXXX

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/s/

CAROLYN L YANCEY

07/13/2012

Review of Final Amendments to the REMS Proposed for Truvada for a Pre-exposure Prophylaxis Indication

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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation IV
Division of Antiviral Products

NDA #:	**21-752**
PRODUCT:	**Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg)**
SPONSOR:	**Gilead Sciences, Inc.**
FROM:	**Kendall A. Marcus, M.D.** **Deputy Director for Safety, DAVP**
DATE:	**July 10, 2012**

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Since Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets was approved on August 2, 2004, we have become aware of the development of resistance-associated substitutions in HIV-1 viral isolates obtained from individuals with unrecognized acute HIV-1 infection who initiated Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for pre-exposure prophylaxis of sexually acquired HIV-1 infection. The development of resistance-associated substitutions was observed in viral isolates obtained from individuals with unrecognized HIV-1 infection who enrolled in the iPrEx and Partners PrEP trials submitted in support of this sNDA application. We have also become aware of the known serious risks of renal and skeletal abnormalities in patients treated with Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for known HIV-1 infection, which must be evaluated in the context of the new patient population treated in the clinical trials submitted in support of this sNDA application. Finally, during review of data submitted in this sNDA, we have become aware of the potential for an unexpected serious risk of adverse maternal-fetal outcomes in women who become pregnant while taking Truvada® for pre-exposure prophylaxis of sexually acquired HIV-1 infection, including risk for HIV seroconversions in mother and infants if Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets is discontinued because of pregnancy, spontaneous miscarriages, and preterm deliveries. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary to ensure that the benefits of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets, for pre-exposure prophylaxis (PrEP) to prevent sexually-acquired HIV infection in adults, outweigh its risks. In reaching this determination we considered the following:

A. The estimated number of individuals in the United States at high risk for sexual acquisition of HIV-1 infection is unknown, however, available data indicate that approximately 50,000 individuals in the United States contract HIV infection each year, predominantly through high risk sexual behavior.[1] The number of at-risk individuals is likely to be at least 10-fold higher, however, a more precise estimate is unknown.

B. HIV infection is a potentially serious and life-threatening condition. Untreated HIV infection significantly decreases life expectancy, often by 30 years or more. Life expectancy is still reduced by about 10 years even when treatment for HIV is successful in suppressing viral replication and increasing CD4+ cell counts to normal levels.

C. Individuals at high risk for sexual acquisition of HIV-1 infection who take Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for pre-exposure prophylaxis in combination with safer sex practices can expect to avoid contracting HIV-1 infection, a serious and potentially life-threatening disease that requires life-long therapy with multidrug antiretroviral regimens.

D. Expected duration of use of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for the PrEP indication is unknown at this time.

E. In the iPrEx and Partners Prep trials submitted to FDA in support of an application for marketing approval of a PrEP indication, a total of ten individuals were enrolled in these trials with unrecognized HIV infection and were assigned to receive Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets or tenofovir for pre-exposure prophylaxis. Five of the ten individuals developed viral strains with resistance to one or more antiretroviral drugs used for treatment, thus significantly limiting their HIV treatment options. In addition to postmarketing reports of resistance development in viral isolates from individuals who initiated Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for PrEP with unrecognized HIV infection, Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets has been associated with various other adverse effects reported by HIV-infected patients taking Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets as part of a complete antiretroviral regimen: lactic acidosis and severe hepatomegaly with steatosis; severe acute exacerbations of hepatitis B in coinfected patients who discontinued Truvada; new onset or worsening renal impairment; decreases in bone mineral density and osteomalacia.

F. Truvada is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR part 208, FDA has determined that a Medication Guide is required for Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) for the PrEP indication. FDA has determined that Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg). FDA has determined that Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) is a product for which patient labeling could help prevent serious adverse effects, that the Medication Guide is important to health and that patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide, an element to assure safe use (prescriber education and training program), and a timetable for submission of assessments of the REMS.

On December 14, 2011, Gilead Sciences, Inc. submitted a supplemental New Drug Application to market Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for pre-exposure prophylaxis of sexually acquired HIV-1 infection in adults at high risk. The application contained a proposed risk evaluation and mitigation strategy (REMS), which included a Medication Guide, a communication plan, an element to assure safe use (ETASU) and a timetable for submission of assessments. Below this memo explains the rationale for changing the elements of that proposed REMS.

The goal of the Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) for the PrEP indication REMS is as follows: to inform and educate prescribers, other healthcare providers (HCP), 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® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants

- The fact that Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets 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

The applicant initially proposed to achieve these goals with the following proposed elements:

- A Medication Guide
- A communication plan consisting of
    - a Dear HCP letter containing the updated Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets label, Medication Guide, and prescriber and patient safety brochure
    - Internet website access for healthcare providers, individuals at high risk for acquiring HIV and peer educators
- "Voluntary" education and training program for prescribers of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for a PrEP indication

- An implementation plan

After further review of the proposed REMS, the Office of Surveillance and Epidemiology and the Division of Antiviral Products are in agreement that the proposed element of the communication plan, consisting of the Dear HCP notification letter and the Internet website, will both be incorporated into the ETASU as part of the prescriber training and education program for healthcare providers. The goal of sending the Dear HCP letter to potential prescribers of Truvada for PrEP is to educate them about the potential and known risks associated with the use of Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for a PrEP indication, the importance of prescribing Truvada® (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) tablets for PrEP as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and to explain how to access the relevant training and education materials provided by Gilead. The goal of establishing a website for potential prescribers of PrEP and individuals taking PrEP is to provide access to training and education about PrEP. As such, both the Dear HCP letter and the website are a component of the education and training program, an ETASU.

In addition, OSE and DAVP are in agreement that the implementation plan is not applicable for this REMS since an implementation system does not apply to healthcare provider training or certification.

Therefore, the approved REMS will include a Medication Guide, elements to assure safe use and a timetable for submission of assessments of the REMS.

[1] Prejean J et al. Estimated HIV incidence in the United States, 2006–2009. PLoS ONE 6(8): e17502.

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/s/

KATHERINE SCHUMANN
07/14/2012

KENDALL A MARCUS
07/14/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Amendments to the Risk Evaluation and Mitigation Strategy (REMS) Proposed for TRUVADA for a Pre-exposure Prophylaxis Indication (Set 3)

Date:	June 21, 2012; *revised June 25, 2012*
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)
	Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Interim Comments on the Amendments to the Risk Evaluation and Mitigation Strategy (REMS) proposed for TRUVADA for a Pre-Exposure Prophylaxis (PrEP) indication for Human Immunodeficiency Virus-1 (HIV-1) infection (Submitted on June 5, 14, and 19, 2012 under Supplement 30)
Drug Name(s):	TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) Tablet
Therapeutic Class:	Nucleoside/Nucleotide (emtricitabine/tenofovir disoproxil fumarate) Analog HIV-1 Reverse Transcriptase Inhibitors
Dosage and Route:	Fixed-dose combination tablet of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine
NDA #/Supplement:	NDA 21-752/ Supplement 30/Sequences 745, 748 and 749)
Applicant:	Gilead Sciences, Inc. (Gilead)
OSE RCM #:	2012-73 (TRUVADA does not have a TSI Number)

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 INTRODUCTION

This Division of Risk Management (DRISK) Interim Comments Review (Set 3) evaluates and communicates required revisions to the amendments to the Risk Evaluation and Mitigation Strategy (REMS) proposed for Truvada for pre-exposure prophylaxis (PrEP) submitted on June 5, 14, and 19, 2012. The Agency sent comments to the applicant on May 30, 2012 based on an amendment to the REMS for Truvada for a PrEP indication (dated May 8, 2012) and on a new required Prescriber Educational Slide Deck (Information Request letter dated June 20, 2012). The initial proposed REMS for Truvada for a PrEP indication was included in supplemental New Drug Application (sNDA) 21-752 submitted on December 15, 2011.

The Prescription Drug User Fee Act (PDUFA) goal date (June 15, 2012 for sNDA 021-752) was extended by three months to provide time for full review of the proposed REMS for Truvada for a PrEP Indication (received on June 5, 2012). The extended user fee goal date is September 14, 2012.

2 MATERIALS REVIEWED

The following materials, listed by document date, reviewed from sNDA 021-752 for TRUVADA for a PrEP indication (Supplement 30), are in regards to amendments to the proposed REMS:

- May 17, 2012: The Agency held a teleconference with the applicant to discuss issues following the Antiviral Drugs Advisory Committee (AVDAC) meeting: labeling, revisions to the REMS, and new required REMS appended materials.
- May 30, 2012: The Agency sent comments based on the DRISK Interim Comments Review, Set 2 (dated May 30, 2012) to the applicant.
- June 4, 2012: The Agency sent a revised REMS Document with additional revisions (inserted into the version dated May 8, 2012/Sequence 740) to the applicant.
- June 5, 2012: Sequence 745 -The applicant submitted an Amendment to the REMS proposed for Truvada for a PrEP indication with revisions and new training and educational materials to the Agency (the REMS Document and REMS website were not included in this submission).
- June 5, 2012: The Agency issued a Review Extension – Efficacy Supplement letter to Gilead notifying them that the Amendment (Sequence 745) prompted extension of the PDUFA goal date to permit full review by the Agency.
- June 14, 2012: Sequence 748 - The applicant submitted an Amendment to the proposed REMS for Truvada for a PrEP indication to the Agency. The submission includes all REMS appended materials except the REMS website.
- June 18, 2012: The Agency sent the applicant three key questions about the proposed observational study and REMS assessments/REMS training and educational materials. Gilead's written response has not been received by the Agency.

- June 19, 2012: Sequence 749 - The applicant submitted an Amendment to the proposed REMS for Truvada for a PrEP indication with a revised TRUVADA REMS website
- June 20, 2012: The Agency sent an Information Request letter to the applicant with comments and required revisions to the Prescriber Educational Slide Deck

Prescribing Information

- May 22, 2012: Sequence 742 - The applicant submitted revised labeling in response to a teleconference with FDA on May 17, 2012 and subsequent labeling comments from FDA on the same day.
- June 8, 2012: Sequence 747 - The applicant submitted revised labeling to FDA.
- June 15, 2012: The Agency sent revised labeling to the applicant.
- June 25, 2012: The Agency sent Gilead changes to the Medication Guide per the Patient Labeling Review (dated June 20, 2012) and revised labeling changes.

FDA Reviews

- May 17, 2012: Office of Prescription Drug Promotion (OPDP), the Division of consumer Drug Promotion (OCDP) Review of the Draft REMS Materials for TRUVADA for a PrEP Indication by Emily Baker, Regulatory Review Officer, DPDP and Kemi Asante, Regulatory Review Officer, DCDP
- June 20, 2012: Patient Labeling Review written by Sharon Mills, BSN, RN, CCRP, Senior Patient Labeling Reviewer, Division of Medical Policy Programs (DMPP)

3 SUMMARY OF THE APPLICANT'S AMENDMENTS TO THE PROPOSED REMS FOR A PRE-EXPOSURE PROPHYLAXIS INDICATION

The applicant submitted amendments to the proposed REMS for TRUVADA for a PrEP indication on June 5, 14, and 19, 2012 based on Agency comments. The following is a description of Gilead's responses to Agency comments.

REMS Document

The applicant accepted all of the Agency's revisions to the REMS Document proposed by the DRISK.

REMS ELEMENTS

Medication Guide

The applicant has not yet submitted a revised Medication Guide.

Comment:

The Patient Labeling Review (dated June 20, 2012) includes track changes that the applicant must incorporate into the Medication Guide. [1]

[1] Patient Labeling Review (dated June 20, 2012) written by Sharon Mills, BSN, RN, CCRP from the Division of Medical Policy Programs (DMPP)

Element to Assure Safe Use (ETASU) - Prescriber Training and Education

The applicant submitted new information and new and/or revised training and educational materials in response to Agency comments. The materials include the following:

- A List of professional organizations designated to disseminate key safety information about TRUVADA for a PrEP indication to likely prescribers
- Journal Information Pieces (to be published quarterly as printed information in five professional journals)
- Agreement Form: Initiating TRUVADA for a PrEP of Sexually Acquired HIV-1 Infection
- Checklist for Prescribers: Initiation of TRUVADA for PrEP
- Prescriber Educational Slide Deck
- REMS website (www.truvadapreprems.com)

Comments:

1. The Prescriber Educational Slide Deck must be revised to reflect comments and track changes from the Division of Antiviral Products (DAVP) (Information Request letter dated June 20, 2012). The required changes are consistent with revised FDA-labeling.
2. The applicant must accept the DRISK required track changes to the following training and educational materials (see **Attachments** in this review):
    - Safety Information Fact Sheet
    - Dear Healthcare Provider letter
    - Important Safety Information about TRUVADA for a PrEP Indication for Healthcare Providers
    - Important Safety Information about TRUVADA for a PrEP Information for Uninfected Individuals
    - Training Guide for Healthcare Prescribers
    - Agreement Form for Initiating TRUVADA for Pre-Exposure Prophylaxis (PrEP) of Sexually Acquired HIV-1 Infection
    - Checklist for Prescribers: Initiation of TRUVADA for PrEP
    - Prescriber Educational Slide Deck (See above Comment #1)
    - REMS program website, www.truvadapreprems.com

Timetable for Submission of Assessments

The applicant accepted all of the DRISK required revisions to the Timetable for Submission of Assessments and this component is acceptable to the DRISK.

Comment:

1. See the REMS Document in **Attachments** in this review.

REMS Assessment

Gilead amended the proposed REMS assessment to report on the following:

1. Number of prescribers who completed the training and educational program via the Gilead website or through mailings
2. Demographics of registered prescribers and uninfected individuals
3. Information on uninfected individuals taking Truvada for a PrEP indication regarding reported compliance with treatment, HIV-1 testing, and risk behavior associated with obtained reports of lack of efficacy, as available.
4. Estimates of the total number of Truvada prescriptions for a PrEP indication via third party vendor(s)
5. Information received from adverse event reporting from spontaneous sources, published literature, regulatory agencies, clinical studies (clinical serious adverse events/SAEs) and solicited sources for entry into the Gilead drug safety database.
6. Updates on a Gilead PrEP registry implemented post-approval of Truvada for a PrEP indication. This registry will be a prospective, multicenter, 3-year observational study of current practices as determined by the healthcare provider (HCP).
7. Gilead will engage a third party vendor to complete the following:
    a. Conduct a web-based phone and paper-based option, self-administered Knowledge, Attitude and Behavior (KAB) survey for prescribers and uninfected individuals taking (or recently taken) Truvada for a PrEP indication. Surveys will assess prescriber and uninfected individuals understanding of the risks associated with use of Truvada for a PrEP indication, understanding the importance of compliance, and risk behavior to assess the effectiveness of the REMS outreach and education.
    b. Gilead will develop and administer these surveys anonymously on a periodic basis to a random sample of uninfected individuals at high risk for acquiring HIV-1 infection currently taking (or who have taken) Truvada for a PrEP indication) and of prescribers who have registered to take the survey.
8. With respect to REMS goals, an assessment of the extent to which the elements are meeting the goals or whether or not the goals or such element should be modified.

Comments:

1. See **Section 5, Comments To Be Sent To The Applicant**, in this review, for additional requirements to the REMS Assessment.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

The DRISK requests that the comments to the appended REMS training and educational materials, and the REMS website in **Section 5**, **Comments To Be Sent To The Applicant,** in this review, be sent to Gilead as soon as possible.

Appended to this review are **Attachments** including required track changes that the applicant must accept as the REMS for TRUVADA for a PrEP Indication. The comments are based on internal FDA discussions about the REMS for TRUVADA for a PrEP indication and consistency with revised labeling.

5 COMMENTS TO BE SENT TO THE APPLICANT

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 (submitted 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 to 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 Information for Uninfected Individuals
        v. Training Guide for Healthcare Prescribers
        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

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, 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

The REMS Supporting Document must be consistent with all changes made to the REMS Document, training and educational materials and REMS assessment. See **Attachments** with recommended minor track changes in the REMS Supporting Document.

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 document 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 be in a single MS Word document.

ATTACHMENTS

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/s/

CAROLYN L YANCEY

06/25/2012

sNDA 021752 TRUVADA for a PrEP Indication/ Supplement 30/ Sequences 745, 748 and 749 (submmited on June 5, 14, and 19, 2012, respectively.

CLAUDIA B MANZO

06/25/2012

concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on the Amendments to the Risk Evaluation and Mitigation Strategy (REMS) Proposed for TRUVADA for a Pre-Exposure Prophylaxis (PrEP) Indication (Set 2)

Date:	May 22, 2012; *Revised May 29, 2012*
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK)
	Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Interim Comments on the Amendments to the Risk Evaluation and Mitigation Strategy (REMS) proposed for TRUVADA for a Pre-Exposure Prophylaxis (PrEP) indication for Human Immunodeficiency Virus-1 (HIV-1) infection (Submitted May 8, 2012/Supplement 30/Sequence 740)
Drug Name(s):	TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) Tablet
Therapeutic Class:	Nucleoside/Nucleotide (emtricitabine/tenofovir disoproxil fumarate) Analog HIV-1 Reverse Transcriptase Inhibitors
Dosage and Route:	Fixed-dose combination tablet of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine
NDA #/Supplement:	NDA 21-752 - Supplement 30/Sequences 704, 721, 724, 732, 737, and 740)
Applicant:	Gilead Sciences, Inc. (Gilead)
OSE RCM #:	2012-73 (TRUVADA does not have a TSI Number)

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 EXECUTIVE SUMMARY

The purpose of this Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) Interim Comments Review, Set 2, is to evaluate and communicate required revisions to the amendments to the Risk Evaluation and Mitigation Strategy (REMS) proposed for Truvada for a pre-exposure prophylaxis (PrEP) indication for sexually transmitted Human Immunodeficiency Virus-1 (HIV-1) infection (submitted on May 8, 2012). The Agency sent comments to the applicant on April 12, 2012[1] based on the initial proposed REMS for Truvada for a PrEP indication included in supplemental New Drug Application (sNDA) 21-752 (submitted on December 15, 2012).

The applicant's amendments to the REMS proposal (dated May 8, 2012) include revised goals, a Medication Guide, an element to assure safe use (ETASU), prescriber training and education not linked to restricted distribution or access to Truvada for a PrEP indication, and a Timetable for Submission of Assessments.

An Antiviral Drugs Advisory Committee (AVDAC) was held on May 10, 2012. The AVDAC recommended that the applicant significantly strengthen the REMS program to include restrictions on access to Truvada for a PrEP indication based on a negative HIV-1 test result and to provide more active and robust prescriber training and education for uninfected individuals considering or taking Truvada for a PrEP indication. (See **Section 7, Appendix,** in this review, for a Summary of the AVDAC Meeting.)

Internal FDA discussions were held following the AVDAC, including a Center Director Debriefing meeting to discuss the the AVDAC recommendations to the REMS for Truvada for a PrEP indication. There was general agreement that the prescriber training and educational materials can be strengthened to more actively educate prescribers and individuals about the known and potentially serious risks with use of Truvada for a PrEP indication. However, the DRISK, the DAVP, senior OSE and Center for Drug Evaluation and Research (CDER) leadership conclude that restrictions on access to Truvada for a PrEP indication are not feasible based on the current availability of Truvada, the moiety, in the United States (US).

The DRISK and the DAVP conclude that there are a number of required revisions to the proposed REMS that must be completed for the REMS to be acceptable to the Agency. See **Section 6, Comments To Be Sent To The Applicant** and **Attachments** (including track changes), in this review. The applicant was informed of the required revisions to the REMS and required new training and educational materials during a teleconference with the Agency on May 17, 2012. The applicant communicated verbal agreement with the REMS revisions and required new materials.

1.1 REGULATORY HISTORY

The Antiviral Drugs Advisory Committee meeting is the key regulatory event since the

[1] Interim comments on the Proposed Risk Evaluation and Mitigation Strategy for TRUVADA for Pre-Exposure Prophylaxis (PrEP) Indication, Set # 1 (dated April 12, 2012) written by Carolyn L. Yancey, M.D., F.A.A.P., DRISK

DRISK Interim Comments Review (Set 1) [1]. See **Section 7**, the **Append**ix, in this review for a Summary of the AVDAC meeting.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials, listed by document date, reviewed from sNDA 021-752 for TRUVADA for a PrEP indication (Supplement 30) in regards to the amendments to the proposed REMS are:

- March 30, 2012: The Agency sent the applicant comments/requirements regarding the proposed REMS for Truvada for a PrEP indication
- March 30, 2012: Sequence 721 - The applicant submitted an Interim "Day 1" website with access to approved REMS materials
- April 18, 2012: The Agency sent the applicant a revised REMS Document with additional revisions made to the version sent to the applicant on March 30, 2012
- April 24, 2012: Sequence 732 - The applicant submitted a Draft Presentation for the FDA Antiviral Products Advisory Committee Meeting
- April 26, 2012: The Agency sent the applicant comments and responses to the proposed REMS that superseded previous comments from the Agency. Comments about the REMS Assessment Plan were also included.
- May 1, 2012: Sequence 737 - The applicant submitted responses to FDA's Comments regarding the Draft Advisory Committee Meeting presentations
- May 8, 2012: Sequence 740 - The applicant submitted an amendment to the proposed REMS for TRUVADA for a PrEP indication including amended REMS appended materials
- May 10, 2012: AVDAC meeting was held on the FDA White Oak Campus in Silver Spring, Maryland
- May 16, 2012: FDA Center Director Debriefing to discuss the AVDAC, the regulatory decision, and the REMS

Prescribing Information

- April 11, 2012: Sequence 724 - The applicant submitted revised Truvada labeling including required terminology revisions and among other revisions applicable to the proposed PrEP indication

FDA Teleconferences

- April 27, 2012: The Agency held at teleconference with the applicant to discuss clinical questions and respond to the applicant's questions about required amendments to the proposed REMS for Truvada for a PrEP indication

- May 17, 2012: The Agency held a teleconference with the applicant to discuss labeling and REMS required revisions including new education and training materials for prescribers and individuals.

Guidelines and Guidances

- Department of Health and Human Services Adult and Adolescent HIV Treatment Guidelines, http://aidsinfo.nih.gov/guidelines (March 2012)
- CDC Interim Guidance on HIV Pre-Exposure Prophylaxis for Men Who Have Sex with Men (February 2011)

3 SUMMARY OF APPLICANT'S AMENDMENTS TO THE PROPOSED REMS FOR TRUVADA FOR A PREP INDICATION

The applicant submitted an amendment to the proposed REMS on May 8, 2012 in sNDA 021-752, Supplement 30/Sequence 740 based on Agency comments on the initial proposed REMS. The amendments to the proposed goals and REMS materials in the REMS for TRUVADA for a PrEP indication include the following:

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Comments:

1. *The applicant agreed to report the following required analyses:*
    - *Drug use data including estimates of the number of prescriptions for Truvada for a PrEP indication, to the extent possible*
    - *Number of prescribers who complete the training*
    - *Prescribers, by specialty type, who prescribe Truvada for a PrEP indication, to the extent possible*
    - *Survey data for prescribers and individuals, to the extent possible*
2. *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.*
3. *The assessment plan should include, to the extent that the sponsor is able to ascertain this information, the following:*
    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*

4 DISCUSSION

The DRISK and the DAVP considered a restricted distribution program for Truvada for a PrEP indication to address the risk of development of drug resistant HIV-1 variants if Truvada is approved for PrEP. A restricted distribution plan for access to Truvada for a PrEP indication would need to encompass the following:

- **Prescriber Certification and Enrollment** in order to prescribe Truvada for a PrEP indication. Prescribers would be required to undergo training and education and would be required to verify a negative HIV-1 test result (**Documentation of Safe Use Conditions**). Individuals taking Truvada for a PrEP indication would need to be enrolled in a registry so that dispensing pharmacies could verify that the individual is eligible for use of Truvada for a PrEP indication. The registry might collect HIV-1 lab test results.
- **Documentation of Safe Use Conditions** would be required in order to dispense the drug for a PrEP indication.
- **Pharmacy Enrollment** would be required. Pharmacists would need to verify enrollment of prescribers as well as enrollment of an individual in the registry and/or verification of the actual HIV-1 test result. This raises a number of privacy issues under the Health Insurance Portability and Accountability Act of 1996 (HIPPA) privacy and security rules.

There is considerable overlap across each required ETASU in a REMS program.

However, a restricted distribution plan for access to Truvada for a PrEP indication is not a feasible option because Truvada is available in the US for the treatment of HIV infection. Any REMS that restricts use to only one indication can be easily circumvented when the moiety is available on the US market.

Alternatively, a tightly controlled program that applies to the drug for any single indication would adversely affect access for patients being treated with Truvada for HIV-1 infection. Such a tightly controlled program would also place tremendous burden on prescribers and pharmacies.

The Agency concurred that a different trade name and/or packaging would not prevent circumventing a restricted REMS program because the drug ingredients and dosage form are the same as Truvada for the treatment of patients with HIV-1 infection. Based on internal FDA discussion, the Division of Medication Error Prevention and Analysis (DMEPA) concurs with this conclusion.

As stated in the previous review [1] and, for the rationale stated above, the DRISK and the DAVP do not believe that drug access should be restricted with the ETASU, Documentation of Safe Use Conditions. However, we recognize the importance of baseline HIV-1 testing and regular HIV-1 testing consistent with the CDC guidelines and the AVDAC recommendations. HIV-1 testing requirements will be included in the BOXED WARNING of labeling and will be emphasized in all of the REMS training and educational materials directed to prescribers and individuals.

The applicant proposes non-REMS supportive measures (opt-in reminder service, free condoms, and subsidized HIV testing for individuals who convert from HIV-1 negative

to HIV-1 positive) and a Medication Assistance Program to be implemented if Truvada for a PrEP indication is approved.

The DRISK and the DAVP agree with the strong and clear message from the AVDAC to strengthen prescriber training and educational materials and improve educational information directed to individuals considering or taking Truvada for a PrEP indication. See **Section 6, Comments To Be Sent To the Applicant**, in this review, for revisions to the REMS Document, required new training and educational materials for prescribers and individuals, and revisions to appended REMS materials including the REMS website.

5 RECOMMENDATIONS FOR THE DIVISION OF ANTIVIRAL PRODUCTS

The DRISK requests that the comments, required revisions and new training and educational materials in **Section 6**, **Comments To Be Sent To The Applicant,** in this review, be sent to Gilead as soon as possible to facilitate review within the Prescription Drug User Fee Act (PDUFA) deadline (June 15, 2012 for sNDA 021-752).

Appended to this review are **Attachment**s including the REMS, appended REMS materials, and the REMS website (each document with track changes) that the applicant must accept as the REMS for Truvada for a PrEP Indication. The comments and required revisions are based on the AVDAC meeting (May 10, 2012), subsequent internal FDA discussions, including a Center Director Debriefing (May 16, 2012) and a teleconference with the applicant (May 17, 2012).

6 COMMENTS TO BE SENT TO THE APPLICANT

The DRISK requests that the DAVP send the following comments to the applicant:

The following are required revisions to the amendments to the REMS proposed for Truvada for a PrEP Indication (submitted on May 8, 2011) 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 1, 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.

Required Terminology Revisions

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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.

7 APPENDIX

Antiviral Drugs Advisory Committee Meeting Summary

The Antiviral Drugs Advisory Committee (AVDAC) of the FDA Center for Drug Evaluation and Research (CDER) convened on May 10, 2012 at the FDA White Oak Campus, in Building 31, the Great Room of the White Oak Conference Center. The AVDAC discussed the efficacy supplement for the new drug application NDA 021-752, TRUVADA (emtricitabine/tenofovir disoproxil fumarate) submitted by Gilead Sciences, Inc. The supplemental application proposes the indication for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.

In addition to the AVDAC voting participants, non-voting guest speakers included Susan Buchbinder, M.D., Lynn A, Paxton, M.D., M.P.H. from the Centers for Disease Control (CDC), and Jeanna M. Piper, M.D. from the National Institute of Health speaker.

There were 5 major questions to the AVDAC of which the first three questions had subparts. Due to extended time in the AVDAC meeting due to lengthy discussion, the AVDAC only vetted the first three major questions.

Question 1: "Does the current application support a favorable risk-benefit assessment adequate to approve Truvada for a PrEP indication, the vote results were:

- In HIV uninfected men who have sex with men?

  YES: 19 NO: 3 ABSTAIN: 0

- In HIV-1 uninfected partners in serodiscordant couples?

  YES: 19 NO: 2 ABSTAIN: 1

- Other individuals at risk for acquiring HIV-1 through sexual activity?

  YES: 12 NO: 8 ABSTAIN: 2

Points in discussion from those who *did not agree* that a favorable risk-benefit assessment had been demonstrated to approve Truvada for a PrEP indication expressed significant concern that there was insufficient efficacy data in Afro-American females. In fact it was noted that not one individual of this minority subgroup was included in either of the two pivotal clinical trials. Other descendants expressed concern that the risk is too great to place uninfected individuals at risk for the known serious risks (in particular, renal and bone events) with Truvada.

Several committee members voiced concern in that it is "unrealistic to uncouple adherence from efficacy". In the iPrEx study, the majority of study participants did not comply with adherence to taking a daily oral tablet and/or practicing safer sex. Elaine Morrato expressed significant reservations with a NO-vote citing "risk mitigation is unresolved" for this proposed indication.

Lauren Wood voted NO for approval because of her concern about significant renal disease including end-stage renal disease in an uninfected "healthy" individual. She explained, "Do no harm" is not consistent with the data presented and that "efficacy is not consistent across the clinical trials." She strongly cited the lack of inclusion of Afro-American females in these studies yet the known risk of end-stage renal disease in Afro-American persons.

The Patient Representative, Marlena Vega, sharply expressed that "patients have to take responsibility". The proposed indication is based on an individual's adherence to a daily

dosage regimen, regular HIV-1 monitoring, consistent follow-up with their physician, and consistently practicing safer sex. She rhetorically asked, "How much control does the doctor actually have over a patient?"

There were vigorous and repeated recommendations that the proposed REMS, viewed as weak, be significantly strengthened to include restrictions on access to Truvada for a PrEP indication and that the REMS be more creative with training and educational tools.

The AVDAC recommendations included:

1. Add Elements to Assure Safe Use:

   -Required Prescriber Enrollment a prescriber registry with required training and education in order to prescribe Truvada for a PrEP indication

   - Documentation of Safe Use as a negative HIV-1 test result to receive Truvada for a PrEP indication

   - Registry for Individuals to track persons taking Truvada for a PrEP indication and link to their HIV-1 test results

   - Pharmacy Enrollment to serve a "hard-stop" for receipt of Truvada for a PrEP indication without a known HIV-1 negative test result

2. REMS educational materials must educate prescribers about the "correct way" to manage an individual taking Truvada for a PrEP indication. Prescribers must explain to individuals about the importance of screening for STIs, Hepatitis B virus and the importance of up-to-date immunizations before starting Truvada for a PrEP indication.

3. Enhance prescriber training and education materials with a scientifically driven, evidence-based program for prescribers.

4. Teach prescribers how to perform sexual risk assessments as part of their training

5. The agency needs to understand the process before approving this new indication for Truvada. Who would actually take Truvada for a PrEP indication? Where are these high risk individuals? The applicant must have prescriber data for marketing so that data could be employed to better assess where the high risk communities are located. Target these communities first for prescriber training and education and education of individuals.

6. Add a Prescriber-Individual Agreement Form with key safety risk messages including the comprehensive program of adherence, regular testing and practicing safer sex. The prescriber would explain this information to the individual. Both parties must sign the Agreement Form maintained in the individual's medical record.

7. Add a Prescriber Checklist as a reminder (in the individual's medical record) for the correct management of an individual taking Truvada for a PrEP indication. Use this toll to "force a conversation" between the prescriber and the individual.

8. Develop a different TRADE NAME and packaging for Truvada for a PrEP indication from Truvada for treatment patients with HIV-1 infection

9. Add text to the BOXED WARNING: include serious risks with Truvada for a PrEP indication, regular HIV-1 testing every 2 to 3 months, importance of screening for STIs, and screening for acute HIV-1 infection to continue taking Truvada for a PrEP indication
10. Add recommendations in labeling for safety laboratory test monitoring with thresholds of, for example, renal function test results (e.g., creatinine clearance). Advise stopping thresholds for key lab test results. Explain the risks of stopping Truvada if a person is Hepatitis B virus positive and the risk of exacerbation of Hep B infection. The committee agreed with emphasizing the importance of vaccination for Hep B, if not completed prior to starting Truvada for a PrEP indication.
11. Emphasize drug-drug interactions in labeling and Medication Guide
12. Require, at a minimum, a negative baseline HIV-1 negative test result to receive Truvada for a PrEP indication. Baseline testing has the greatest benefit to avoid an HIV-1 positive person receiving Truvada for a PrEP indication and risking development of drug resistant variants.
13. Recommend a preferred HIV-1 test for screening and recommend when to re-screen individuals (antibody test versus viral load measurement)
14. Consider more frequent monitoring in the first 6-months of starting Truvada for a PrEP indication. Increased frequency of interface (plus required HIV-1 testing) in the early months reinforces behavior adherence (common approach in teaching)
15. Add a requirement for a screening bone mineral density (DEXA Scan) at baseline in high risk individuals for osteopenia. Some committee members did not value a DEXA Scan as highly as other measures, for example, alkaline phosphatase to monitor bone health.
16. Add specific counseling to required prescriber training and education with enrollment
17. Incorporate electronic reminders for regular HIV-1 testing.
18. Create a Pre-Exposure Prophylaxis ICD-10 Code to identify persons taking Truvada for a PrEP indication. This step would support a more accurate analyses in the REMS assessment for drug use data by individuals and prescriber
19. Limit supply of a Truvada prescription (for a PrEP indication) to 90 days (under an ETASU for Pharmacy Enrollment)
20. Use pharmacy data for demographics, to the extent possible, to target communities with highest risks for HIV-1 transmission
21. Surveys in the assessment are understandable but FDA needs more than prescriber and individual surveys. The agency needs a “real demonstration project not a clinical trial.”
22. Require post-marketing studies to track baseline-screening, adherence to the dosage regimen, regular HIV-1 testing every 2 to 3 months. Assess the need for ongoing PrEP in an individual.

23. Resistance-testing should be part of the REMS Assessment

The Chairperson, Judith Feinberg, characterized the proposed REMS program as "passive" clarifying that the "potential harm here is stupendous". Several other members supported this perspective. There was lengthy discussion about a restricted versus non-restricted REMS for Truvada with support for both perspectives, restrictive versus non-restrictive.

There was strong voice from several committee members who opposed restrictions at launch for this proposed indication. In contrast, at least three voting members recommend an unrestricted program at launch, and, based on post-marketing data/demonstration project results, more restrictions could be required later if the first and second REMS assessments appear inadequate for the known serious safety risks with Truvada for a PrEP indication.

The applicant presented supportive programs and materials (not included in the required REMS program) such as an *opt-in reminder service for regular HIV-1 testing*, *free vouchers for condoms,* and *free vouchers for subsidized testing for individuals who seroconvert from HIV-1 negative to positive.*

The FDA clarified to the AVDAC the challenges with any restrictions, regardless of which ETASU or how many ETASU would be implemented, based on the availability of Truvada, the moiety, on the US market, and therefore, the ability of an individual or prescriber to circumvent any restriction.

Question 2:

Discuss the laboratory testing during administration of TRUVADA for a PrEP indication.

The AVDAC responses varied from requiring, at a minimum, a baseline HIV negative test result prior to starting Truvada for a PrEP indication, to more frequent testing only in the first 6-months of taking Truvada for a PrEP indication, to regular monitoring every 2 to 3 months. Some proposed HIV testing every 6 moths for responsible individuals (of course, based on the prescriber's decision). As discussed above, restrictions including a negative HIV test result were vetted by the AVDAC. Discussion about which screening test was not resolved; however, in general, the antibody screening test received reasonable support for regular HIV monitoring.

Additional recommendations for laboratory testing included:

- Hepatitis B screening at baseline
- Baseline renal functions including creatinine clearance, urine dipstix may be inadequate
- Screening foe STIs
- Bone mineral density test (DEXA scan)
- Periodic monitoring for drug resistance variants (no frequency was proposed)

Question 3:

Please comment on the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS).

The perspective from the Chairperson and several vocal committee members was that the proposed REMS is "passive" and must be more active and strengthened for prescriber training and education about the correct management of an individual considering and/or taking Truvada for a PrEP indication. See the recommendations to improve the REMS listed under Question 1.

ATTACHMENTS

Note:

REMS Document to be sent under separate communication from the Agency.

Appended REMS Materials in WORD format only include the Dear Healthcare Provider letter (with track changes)

Appended REMS Materials in PDF cannot be inserted into this WORD document and will be sent separately by the Division of Antiviral Products. The PDF versions include required edits from the Agency.

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/s/

CAROLYN L YANCEY
05/29/2012
Interim Comments Review, Set 2, REMS proposed for TRUVADA for a PrEP indication

CLAUDIA B MANZO
05/30/2012
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on the Proposed Risk Evaluation and Mitigation Strategy for TRUVADA for Pre-Exposure Prophylaxis (PrEP) Indication (Set #1)

Date:	March 14, 2012; *Revised April 12, 2012*
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK) Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Interim Comments on the proposed Risk Evaluation and Mitigation Strategy (REMS) for TRUVADA for a Pre-Exposure Prophylaxis (PrEP) Indication for Human Immunodeficiency Virus-1 (HIV-1) infection (submitted December 15, 2011/Supplement 30/Sequence 704/eCTD Sequence 0390)
Drug Name(s):	TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) Tablet
Therapeutic Class:	Nucleoside Analog HIV-1 Reverse Transcriptase Inhibitor
Dosage and Route:	Fixed-dose combination tablet of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine
Application Type/Number:	NDA 21-752 (Supplement 30/Sequence 704) - Proposed REMS for Truvada for a PrEP indication for HIV-1 infection
Applicant:	Gilead Sciences, Inc. (Gilead)
OSE RCM:	2012-73 (TRUVADA® does not have a TSI #)

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 EXECUTIVE SUMMARY

The purpose of this Office of Surveillance and Epidemiology (OSE), Division of Risk Management Review (DRISK) interim comments review is to evaluate and communicate required revisions to the proposed Risk Evaluation and Mitigation Strategy (REMS) for TRUVADA for a pre-exposure prophylaxis (PrEP) indication for Human Immunodeficiency Virus (HIV-1) infection. The proposed REMS for TRUVADA was submitted on December 15, 2011 for a PrEP indication in sexually active adults [1] and is based on many internal FDA discussions prior to submission of sNDA 21-752 and on stakeholder feedback from an Industry Forum for Collaborative HIV Research (See **Section 7**, **Appendices, Appendix A.**, in this review).

The applicant's REMS for TRUVADA for PrEP indication includes a Medication Guide, a communication plan focused on education and outreach to healthcare prescribers most likely to prescribe TRUVADA for PrEP indication, prescriber training and education as an element to assure safe use (ETASU) not linked to distribution, an implementation plan, and a Timetable for Submission of Assessments.

The applicant's REMS goals are to reduce the risk of acquiring HIV-1 infection. However, the proposed REMS does not include a registry, required monitoring, or restriction to drug access based on documentation of safe use conditions (e.g., a negative HIV test result). The applicant's proposed REMS goals, as submitted, would require at least one of the above components for implementation.

Based on internal meetings and stakeholder feedback, the DRISK and DAVP conclude that a REMS for Truvada for a PrEP indication must include a Medication Guide, ongoing prescriber training and education because the serious risk of acquiring HIV-1 infection while continuing to take Truvada for a PrEP indication and then developing drug resistant HIV-1 variants is an ongoing risk. The DRISK and DAVP do not believe that drug access should be restricted to only trained prescribers or to uninfected individuals with documentation of safe use conditions.

Documentation of safe use (e.g., a negative HIV-1 test result) prior to receiving the drug is not being required because it will likely restrict access for patients with established HIV-1 infection who are being treated with Truvada and two other concomitant antiretroviral medications, and negatively impact adherence for uninfected individuals taking Truvada for a PrEP indication. We also heard stakeholder feedback against mandated laboratory test monitoring.

While the applicant's proposal is aligned with our conclusions, the proposed REMS requires substantial revisions to the applicant's proposed goals, REMS elements, and the appended REMS materials (including the REMS website) to be acceptable to the DRISK and DAVP. See **Section 6. Comments To Be Sent To The Applicant.**

1.1 REGULATORY HISTORY

[1] Sexually active adults are defined as men who have sex with men (MSM) and heterosexual serodiscordant couples.

The key regulatory history that relates to the applicant's REMS for Truvada for a PrEP Indication is summarized in **Section 7**, **Appendices, Appendix A.,** in this review.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials, listed by document date, were reviewed from IND 108,930 for Truvada/Viread and sNDA 21-752 (Supplement 30/Sequence 704) Truvada for a PrEP indication in regard to the proposed REMS:

- November 16, 2011: Agency sent FAX (under IND 108,930) to Gilead with recommendations for a proposed REMS for TRUVADA for a PrEP indication
- December 15, 2011: (Supplement 30/Sequence 704) Applicant submitted sNDA 21-752 for TRUVADA for a PrEP indication in MSM and heterosexual discordant couples
- January 23,2012: (Supplement 30/Sequence 706) the applicant submitted Harmonization of Safety Labeling change with Viread and Emtriva regarding autoimmune disease.
- February 10, 2012: (Supplement 30/Sequence 709) The applicant submitted a proposed REMS website (www.truvadaprep.com)

See **Section 7, Appendices, Appendix A.,** for the regulatory history that relates to the comments included in this review.

3 SUMMARY OF APPLICANT'S REMS FOR TRUVADA FOR A PROPOSED PREP INDICATION

The applicant submitted a proposed REMS with the supplemental NDA 21-752 on December 15, 2011. The proposed goals and REMS elements in the *REMS for Truvada PrEP* included the following:

I. GOALS

The Risk Evaluation and Mitigation Strategy (REMS) goals for Truvada® pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1 are:

1. To educate individuals at high risk for acquiring HIV-1 so they can make informed benefit-risk decisions regarding the use of Truvada PrEP to reduce the risk of acquiring HIV when taken as part of a comprehensive program.
2. To inform prescribers and other health care professionals (HCPs), as well as individuals at high risk for acquiring HIV-1 that Truvada PrEP may not always prevent acquisition of HIV-1 and must be considered as part of a comprehensive prevention strategy in order to reduce the risk of HIV-1 infection.
3. To inform HCPs and individuals regarding the necessity of strict adherence to treatment regimen since prophylactic effectiveness is strongly correlated with adherence to treatment regimen.
4. To reduce the risk of developing resistant HIV-1 variants

a. Truvada must only be taken for pre-exposure prophylaxis of HIV-1 infection by individuals at high risk for acquiring HIV who are HIV negative

b. Regular physician-determined, patient-appropriate HIV testing is recommended while individuals at high risk for acquiring HIV are taking Truvada PrEP to reduce the risk of HIV acquisition

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide is proposed to be dispensed with each Truvada prescription in accordance with 21 CFR 208.24.

B. Communication Plan

The applicant proposed to implement a communication plan that focuses on education and outreach to prescribers and other health care professionals about the safety risks for uninfected individuals considering taking Truvada PrEP. The following materials are proposed as part of the communication plan:

- Prescriber Notification letter about Truvada PrEP, Full Prescribing Labeling
- Prescriber Education Materials
- Option for prescribers to register on-line and obtain access to educational materials (*undefined*) for a clinic setting and receive vouchers for free condoms for individuals at high risk of HIV-1 infection
- Internet website access for healthcare professionals, uninfected individuals at high risk for acquiring HIV infection, and peer educators (*undefined*)
- Safety Brochures for prescribers and uninfected individuals considering taking Truvada for a PrEP indication
- Training Guide for Healthcare Providers
- Truvada Wallet Card
- Interim Guidance for Physicians: CDC Interim Guidance on HIV Pre-Exposure Prophylaxis for Men Who Have Sex with Men
- Uninfected Individual Wallet Card
- Information for peer educators (*undefined*)
- Vouchers free condoms
- Vouchers for subsidized HIV testing to appropriate uninfected individuals
- Assistance with subsidized HIV viral resistance testing in an individual who seroconverts to HIV positive
- Educational materials for a clinic setting (*undefined*)

- Opt-In Reminder Service (*undefined*) for HIV testing for uninfected individuals taking Truvada PrEP
    - Anonymous database to receive reminders regarding the requirement for HIV testing while taking Truvada PrEP
    - Updated information regarding risks associated with Truvada PrEP
- Knowledge, Attitude and Behavior (KAB) Survey access for prescribers and patients (voluntary, anonymous KAB Survey)
- "Appropriate Use" Program including subsidy for HIV-1 testing and STD testing (*undefined*)

C. Element to Assure Safe Use

The applicant proposed to implement an element to assure safe use (ETASU) that will be comprised of voluntary prescriber training and education that will be available via the Truvada PrEP website or, upon request, as paper copy to all potential prescribers of Truvada PrEP.

D. Implementation Plan

Voluntary prescriber training and education is proposed to be available with the launch of Truvada for a PrEP indication, if approved.

E. Timetable for Submission of Assessments

The applicant proposed to submit the REMS assessments to the FDA at 1 year, 3 years and 7 years from the date of initial approval of the REMS, if approved. The assessment will include results of survey responses received and any adverse event information received involving the use of Truvada PrEP. The assessment will also include an analysis of the number of prescribers who have undergone training through the Truvada PrEP website and/or requested a paper copy of the training material.

REMS Assessment Plan

Gilead proposed a REMS Assessment Plan that will report on the following:

1. Demographics of registered prescribers and patients
2. Estimates of the number of Truvada prescriptions for a PrEP indication
3. Number of prescribers who received training via the Gilead website or through mailings
4. Results from the web-based, self-administered KAB survey for prescribers who prescribed Truvada PrEP targeting prescriber's KAB about the key risk messages for HIV-1 testing, compliance with the comprehensive program, and risk behavior to assess the effectiveness of the REMS outreach and education
5. Results of patients' understanding of the risks associated with Truvada PrEP based on prescriber counseling and understanding of the Medication Guide.
6. Information on individuals taking Truvada PrEP to reduce the risk of acquiring HIV-1 infection, reported compliance with treatment, HIV-1 testing, and risk behavior associated with reports of lack of efficacy

7. With respect to the REMS goals, as assessment of the extent to which the elements are meeting the goals or whether the goals and/or elements should be modified

Gilead proposes to contract with a third-party vendor to:

- Develop and administer surveys anonymously on a periodic basis to a random sample of individuals at high risk for acquiring HIV-1 taking or who have taken Truvada for PrEP indication as part of a comprehensive program to help reduce the risk of acquiring HIV-1
- Identify prescribers who have registered to take the survey

The applicant acknowledged that they were asked (by the Agency) to develop benchmarks to assess the number of prescribers who should undergo training for a PrEP indication. The applicant responded that, "it is possible to estimate the number of Truvada prescriptions but more difficult to determine the specific indication for which it (Truvada) was prescribed. In consideration of the proposed voluntary training and education program, the applicant concluded there is "not a process to directly connect all prescriptions to specific prescribers or patients, as is the case with a closed distribution system or mandatory training and certification program".

The applicant developed an indirect method of estimating the prescriptions for non-HIV infected individuals by using proposed available pharmacy vendor data for concomitant medications. The applicant reports that the current use of Truvada for non-HIV or Hepatitis B Virus (HBV) infected individuals is less than (b)(4)%.

Gilead states that a multidisciplinary Review Committee, including senior representatives from Gilead, will review compiled data and evaluate the effectiveness of the REMS. The Committee will identify areas for improvement, if required.

4 DISCUSSION

The DRISK concludes that while some basic components of the proposed REMS are acceptable to retain, substantive revisions to the applicant's proposed REMS for Truvada for a PrEP indication (submitted December 15, 2011) including to the proposed goals, REMS elements, appended REMS materials, the REMS website landing page and the web page links are required to be acceptable. The DRISK and DAVP agree that the proposed REMS must be revised to adequately address the serious risk of development of HIV-1 variants if seroconversion from HIV-1 negative to HIV-1 positive occurs while continuing to take Truvada for a PrEP indication.

The DRISK and DAVP do not believe that drug access should be restricted to only trained prescribes or to individuals with documentation of safe use conditions. Documentation of safe use conditions (e.g., a negative HIV-1 test result) prior to receiving Truvada for a PrEP indication is not being required as it will likely restrict patient access for patients being treated for established HIV infection and negatively impact adherence for individuals taking Truvada for a PrEP indication. We also heard stakeholder feedback against mandated lab monitoring.

Internal discussions, external stakeholder feedback, and discussion at the REMS Oversight Committee (ROC) meeting support this position and rationale.

The ROC meeting (on March 2, 2012) included the following key discussion:

- Agreement with the DRISK/DAVP recommendations for revised goals, REMS elements, and appended REMS materials. The revised REMS elements include:
    - Medication Guide
    - Communication of safety information to key professional organizations with outreach to likely prescribers for Truvada for PrEP indication
    - Ongoing prescriber training and education (ETASU A) for prescribers of Truvada for a PrEP indication. Training would not be required by prescribers in order to write prescriptions for Truvada for a PrEP indication
- Concern about what metrics will be employed in the REMS assessment and how challenging it will be to capture metrics for use of Truvada for a PrEP indication, if approved, as there is no ICD-9 code for uninfected individuals.
- Acknowledgement that if drug use data is low and there are no new safety signals in postmarketing pharmacovigilance, the Agency may conclude that it would not be necessary to continue to require a REMS for Truvada for a PrEP indication.
- Concern about whether or not a generic company would be eligible to apply for a Truvada indication for a PrEP in uninfected individuals.

See **Section 7, Appendices, Appendix B.,** the ROC Summary Package for the REMS for Truvada for a PrEP indication that documents the risk benefit concerns and recommended revisions to the applicant's REMS for Truvada for a PrEP Indication.

Subsequent to the ROC meeting, internal communications clarified the following:

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- Gilead is not eligible for exclusivity for the proposed Truvada for a PrEP indication, if approved, based on the following:
    1. Gilead did not conduct or support 50 % or more the clinical trials submitted in sNDA 21-752 or the costs.
    2. Gilead was not a sponsor of IND 108, 930 Truvada® and Viread®.
- If Truvada for a PrEP indication is approved, there could potentially be generic products for a PrEP indication.

5 RECOMMENDATIONS FOR THE DIVISION OF ANTIVIRAL PRODUCTS

The DRISK requests that the comments, clarifications, and questions in **Section 6, Comments To Be Sent to the Applicant**, in this review, be sent to the applicant as soon as possible to facilitate ongoing review within the Prescription Drug User Fee Act (PDUFA) deadline (June 15, 2012 for sNDA 21-752). Appended to this review is an **Attachment** that the applicant must accept as the REMS for Truvada for a PrEP Indication. The applicant must be reminded that the REMS Supporting Document must be consistent with all revisions to the REMS Document.

6 COMMENTS TO BE SENT TO THE APPLICANT

The following are required revisions to the proposed REMS for Truvada for a PrEP Indication (submitted on December 15, 2011) that must be completed by the applicant. The DRISK requests that the DAVP send the following comments to the applicant:

The Agency concludes that there are substantial required revisions to the proposed REMS for Truvada for a PrEP indication (submitted December 15, 2011/Supplement 30/ Sequence 704). The rationale for each revision is included in the comments. See the **Attachment** and Agency comments below:

Required Terminology Revisions

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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.

7 APPENDICES

Appendix A. Regulatory History

The regulatory history that relates to the proposed REMS for Truvada for a PrEP Indication is as follows:

- June 10, 2011: FDA Regulatory Briefing to discuss a proposed REMS for Truvada for a PrEP Indication (see **Appendices, B.,** ROC Summary Package - REMS for Truvada for a PrEP Indication)
- July 14, 2011: FDA Center Director Briefing to discuss the efficacy, safety, and proposed REMS for Truvada for a PrEP Indication under IND 108.930 (Truvada

and Viread), (see **Appendices, B.,** ROC Summary Package - REMS for Truvada for a PrEP Indication)

- August 19, 2011: Industry Forum - Collaborative Forum for HIV Research (see Meeting Minutes)
- November 10, 2011: The DAVP/DRISK discussed comments to be communicated to Gilead about a proposed REMS in the forthcoming sNDA submission.
- November 17, 2011: The DAVP and DRISK held a teleconference with Gilead to discuss the Agency's comments (dated November 16, 2011)
- January 23, 2012: (Supplement 31) The applicant submitted a New Labeling Supplement with a new safety signal, immune reconstitution syndrome.
- March 2, 2012: Agency ROC meeting - the committee agreed with DRISK/DAVP recommended revisions to the REMS goals, REMS elements, and appended materials including deletion of specific materials and/or services that appear promotional. Jane Axelrad underscored the need to inquire if any ANDAs are under review. See **Section 4**, **Discussion and Recommendations to DAVP**, in this review for details concerning a pending ANDA.
- March 14, 2012: Mid-Cycle for Truvada for a PrEP Indication

Appendix B. ROC Summary Package - REMS for Truvada for a PrEP Indication

To: Risk Oversight Committee (ROC)

In view of possibly not convening a face-to-face meeting, priority review status of this efficacy supplement, and a limited timeframe within which to inform the applicant about revisions to the proposed REMS, review their responses, and allow for the clearance process, please see the following summary and questions at the end of this document.

Efficacy Supplement NDA 21752 (Sequence 030)

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) Tablet

Introduction

The applicant, Gilead Sciences Ltd., submitted NDA 21-752 for TRUVADA (a fixed-dose combination tablet of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine) as an efficacy supplement in support of the proposed use of TRUVADA® for pre-exposure prophylaxis (PrEP) of Human Immunodeficiency Virus-1 (HIV-1) infection in *uninfected individuals* at high-risk for contracting HIV-1 infection. Two Phase 3 clinical studies submitted to support the proposed use of TRUVADA for a PrEP indication are:

- **CO-US-104-0288**: "Chemoprophylaxis for HIV Prevention in Men", also known as the Pre-Exposure Prophylaxis Initiative or "iPrEX" Study

- **CO-US-104-0380**: "Parallel Comparison of Tenofovir and Emtricitabine/ Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples"

There are two proposed target populations for TRUVADA for the PrEP indication:

- Men who have sex with men (MSM)
- Heterosexual discordant couples

There are no approved drugs in the US or globally for a PrEP indication of HIV-1 infection.

The DAVP recommended that the applicant submit a risk evaluation and mitigation strategy (REMS) to address the risks of drug resistant development of HIV-1 variants if TRUVADA for the proposed PrEP indication is not administered in a comprehensive treatment program with strict adherence to regular HIV testing and behavior education to reinforce the important need for safer sex practices.

The DRISK and DAVP are aligned from discussion in the Regulatory Briefing (June 10, 2011) and the Center Director Briefing (July 14, 2011), that a REMS appears to be necessary for TRUVADA for the proposed PrEP indication, but that a REMS is not necessary for the approved TRUVADA indication for patients with HIV infection.

Brief Background

Tenofovir disoproxil furmarate (VIREAD®) is a nucleoside reverse transcriptase inhibitor. In 2001, the Agency approved TRUVADA® (emtricitabine/VIREAD®) for the treatment of established HIV infection. The approved and marketed indication and usage of TRUVADA® is:

- In a combination of EMTRIVA and VIREAD, both nucleoside analog HIV-1 reverse transcriptase inhibitors, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

Generics

- There are no approved generics for TRUVADA or VIREAD in the United States (US)
- **US President's Emergency Plan for AIDS Relief**

  Under the US President's Emergency Plan for AIDS Relief (PEPFAR) to help save the lives of those suffering from HIV/AIDS around the world, there are generic copies of previously authorized antiretroviral products in the US that are new combinations or regimens made available to non-US developing countries through PEPFAR programs.

Packaging

- The proposed packaging and container for TRUVADA® for the proposed PrEP indication is identical to the marketed TRUVADA® for patients with HIV infection.

Past Meetings Focused on the Proposed TRUVADA indication for PrEP

- June 10, 2011: A **Regulatory Briefing** included discussion of known and potential safety risks in the context of TRUVADA for PrEP indication in *uninfected individuals*, potential REMS Elements in the context of the importance of adherence to the TRUVADA for PrEP indication dosing regimen, HIV testing and follow-up, and the challenges of compliance in high-risk populations. Restricted distribution and/or required HIV testing for drug access do not appear feasible as both drugs in TRUVADA are approved in the US. Prescribers and individuals considering TRUVADA for the PrEP indication could circumvent a REMS program to obtain TRUVADA for the PrEP indication. A restrictive program could negatively impact access for patients being treated for HIV-1 infection. Additionally, it was pointed out that FDA has never restricted distribution of a product because of concerns of emergence and spread of resistant organisms. For example, we know that some HIV-infected patients will develop and spread resistant virus, but we do not restrict access or require documentation of proper use to obtain antiretroviral drugs.
- July 14, 2011: The **Center Director Briefing** included discussion of publically released information about the iPrEX study results (MSM), the Partnership PrEP study results (heterosexuals), and the CDC TDF2 study results (heterosexuals). Slides presented included the applicant's 1) proposed REMS for TRUVADA for the PrEP indication in MSM with goals, 2) proposed REMS elements as a Medication Guide and a communication plan, 3) a PrEP website with education materials, and 4) Non-REMS programs to include the CDC Demonstration project. Discussion focused on the importance of a potential REMS to inform and educate prescribers and *uninfected individuals* considering treatment with TRUVADA for the PrEP indication about the importance of strict adherence to the labeled recommendations as part of a comprehensive treatment program that includes regular HIV testing and behavior education to reinforce the need for safer sex practices. The discussion included the following suggestions:
    - Add heterosexual discordant couples *and* MSM to the proposed target population for TRUVADA for the PrEP indication
    - Because of the approved TRUVADA treatment, in combination with other antiretroviral drugs, for established HIV infection, a potential REMS for TRUVADA for the proposed PrEP indication should not be linked to the ability to prescribe or dispense the drug.
    - A proposed REMS for TRUVADA for the PrEP indication would potentially include only one ETASU, prescriber training and education as a voluntary element for prescribers
    - Additional considerations included:
        - The key goals of a proposed REMS could be to inform and educate prescribers and *uninfected individuals* considering or taking TRUVADA for the PrEP indication about the risks associated with use of TRUVADA if treatment and safer sex behavior is not adhered to as recommended in a comprehensive program.

        - A proposed REMS assessment would not be able to assess the impact of TRUVADA drug resistance development to HIV-1 infection because there would be no restricted drug distribution, no mandatory documentation of safe use (regular HIV-1 testing with follow-up confirmation of a negative HIV-1 result), and no registry of prescribers or *uninfected individuals* taking TRUVADA for a proposed PrEP indication.
        - A proposed REMS assessment could assess prescribers' and *uninfected individuals'* understanding of the importance of strict adherence to the recommendations for taking TRUVADA for the proposed PrEP indication to reduce the risk of drug resistant development of HIV-1 variants.

- August 19, 2011: An **Industry Forum for Collaborative HIV Research** included a full day of panel discussion (and audience participation) on diverse topics. Discussion that pertained to risk mitigation strategy included the following:
    - Stakeholders overwhelmingly concurred that any restricted drug distribution, mandatory or voluntary registry for prescribers or *uninfected individuals* taking TRUVADA for the PrEP indication, and/or documentation of safe use (HIV-1 negative test result) would not be a successful risk mitigation strategy because the two drugs contained in TRUVADA are approved products in the US market. Stakeholders appeared to be aligned with concern that prescribers and healthy individuals could circumvent a restricted risk mitigation program making such a program ineffective to mitigate the risks
    - Stakeholders voiced that a proposed TRUVADA for a PrEP indication education and outreach program should be considered in the context of larger HIV prevention initiatives to reduce the number of individuals who become HIV-1 infected each year
    - Stakeholders suggested that postmarketing surveillance carefully monitor the safety risks and drug resistant variants, to the extent possible.

Regulatory Timelines

- November 16, 2011: FAX from the DAVP and the DRISK to Gilead with comments about a proposed REMS for TRUVADA for the PrEP indication
- December 15, 2011: Applicant submitted the efficacy supplement NDA 21-752 TRUVADA for the PrEP indication (SN-0390), Priority Review
- March 5, 2012: Risk Oversight Committee (ROC) Meeting
- March 14, 2012: Mid-Cycle Meeting
- May 10, 2012: Advisory Committee meeting (One-Day)
- June 15, 2012: PDUFA Action Date

Summary of Safety

In consideration of clinical safety data from the iPrex and Partner PrEP studies, in addition to the known safety profile of TRUVADA in the treatment of HIV-1 infection, see the following potential safety risks associated with use of TRUVADA for the PrEP indication:

- HIV-1 Acquisition: TRUVADA for the PrEP indication may not always prevent HIV-1 infection, even when there is adherence to the dosing regimen and other preventive strategies
- Development of TRUVADA Resistance: Resistant HIV-1 variants may emerge in *healthy individuals* with unrecognized HIV-1 infection who continue to take TRUVADA for the PrEP to reduce the risk of acquiring HIV-1
- Additional safety issues per TRUVADA labeling:
    - Post-treatment exacerbation of Hepatitis B in Hep B Virus Mono-Infected individuals: Severe acute exacerbations of Hepatitis B virus may occur upon discontinuation of TRUVADA in individuals treated with TRUVADA for HIV-1 pre-exposure prophylaxis who are infected with Hepatitis B virus
    - Other Potential Safety Risks is Uninfected Individuals:
        - New onset or worsening renal function - creatinine elevations
        - Decrease in bone mineral density and potential risk of increased fractures

Applicant's Proposed REMS for TRUVADA PrEP

Gilead submitted a proposed REMS for TRUVADA for the PrEP indication that includes:

- A Medication Guide
- Communication plan focused on education and outreach to healthcare prescribers and *uninfected individuals*
- Element to Assure Safe Use (ETASU) for Prescriber Training and Education (as a voluntary element)
- Implementation Plan
- Timetable for Submission of Assessments

Applicant's Proposed GOALS

The applicant's proposed Goals in the REMS for TRUVADA for the PrEP indication are to reduce the risk of acquiring HIV-1 infection and drug resistant development of HIV-1 variants (See the **Attachment**). As the proposed REMS for TRUVADA for the PrEP indication does not include restricted drug distribution, registries for prescribers or *uninfected individuals* taking TRUVADA for the PrEP indication, and no required documentation of safe use (a negative HIV test result), the DRISK and the DAVP are aligned that these goals would not be achievable or appropriate under the proposed

program. The DRISK and the DAVP are in agreement that the revised proposed goals must be concise and aligned with the proposed REMS Elements and the REMS assessments.

DRISK and DAVP Revised Proposed GOALS

I. Goals

The goals of the TRUVADA® Pre-Exposure Prophylaxis (PrEP) REMS are:

- To inform and educate prescribers, other healthcare professionals, and individuals at high risk for acquiring HIV-1 about:
    - The importance of strict adherence to the recommendations for taking TRUVADA® PrEP to reduce the risk of development of resistant HIV-1 variants
    - That TRUVADA® PrEP may not always prevent acquisition of HIV-1 infection
    - That TRUVADA® PrEP must be considered as part of a comprehensive prevention strategy in order to reduce the risk of HIV-1 infection.

REMS Elements

Applicant's Proposed Communication Plan

The applicant's proposed communication plan and materials include:

- Prescriber Notification letter about TRUVADA® for the PrEP indication, labeling, a Medication Guide
- Safety brochures for prescribers and *uninfected individual* considering or taking TRUVADA for the PrEP indication
- Educational materials for prescribers
- Information for peer educators (yet undefined)
- Vouchers for free condoms
- Vouchers for subsidized HIV-1 testing to appropriate patients (yet undefined)
- Assistance with subsidized HIV-1 viral resistance testing in an individual who seroconverts to HIV-positive
- TRUVADA Wallet Card
- Educational materials for a clinic setting
- *Opt-In Reminder Service* (for HIV testing) is also proposed in the communication plan materials

The applicant's proposed communication plan targets the following potential prescribers: infectious disease specialists, family practice physicians, internal medicine specialists, obstetricians-gynecologists, STD clinics, and community health clinics. The DRISK and

the DAVP propose to remove “STD clinic” and “community clinic” as these terms are non-specific and require clarification from the applicant. The DRISK and DAVP propose to include emergency medicine physicians and addiction specialists.

The applicant’s communication plan is silent on a dissemination plan for the proposed materials. The DRISK and DAVP alignment includes a communication plan that would target key professional organizations with outreach likely to prescribers of TRUVADA for the PrEP indication.

Applicant’s Proposed ETASU

The applicant’s proposed ETASU is “voluntary prescriber training and education available via the TRUVADA PrEP website or, upon request, as a paper copy to all potential prescribers of TRUVADA PrEP”.

DRISK and DAVP Revised Proposed REMS for TRUVADA PrEP

The DRISK and DAVP are aligned with proposed revisions to the REMS for TRUVADA for the PrEP indication to include a Medication Guide, Communication Plan, ETASU for prescriber training and education (as a voluntary element), and a Timetable for Submission of Assessments. An implementation system is not required for the ETASU, prescriber training and education.

The DRISK and DAVP are aligned with the revised proposed REMS for TRUVADA® for the PrEP indication as summarized in **Table 1**.

Table 1. DRISK Revised Proposed REMS for TRUVADA® PrEP

Revised Proposed REMS Elements	Revised Proposed Content
A. Medication Guide	*Pending Labeling*
B. Communication Plan (CP)	- Communication to key professional organizations that reach targeted prescribers for TRUVADA for PrEP [for example, HIV Medicine Association (HIVMA)] - Dissemination Plan (via email and mailings) every 6 months for 3 years - Move specific CP materials for prescriber education and training to the ETASU - Prescriber Training and Education - Delete other specific CP materials from the proposed REMS
C. ETASU: Prescriber Training and Education (as a voluntary element)	- Prescriber education and training materials (via website and mail) - Materials for *uninfected individuals*

	considering or taking TRUVADA® for the PrEP indication that prescribers will explain and give to these persons
D. Timetable for Submission of Assessments	- Proposed assessments at 1 year, 3 years, and 7 years *(TBD)*
	- Consider a 6 month assessment of the # prescribers (by specialty) targeted for training and education and use of TRUVADA® for the PrEP indication

The DRISK and DAVP are aligned with specific proposed materials/services (see **Table 2.** below) being deleted from a proposed REMS for TRUVADA for the PrEP indication. The applicant could elect to use these materials/services outside of a proposed REMS. The rationale for this alignment is that these specific proposed materials/services do not appear necessary in a proposed REMS for TRUVADA for the PrEP indication to ensure that the benefits outweigh the risks.

Table 2.

Proposed Materials and Services considered for Removal from a proposed REMS for TRUVADA for the PrEP indication

Component	**Issues and Clarifications**
Peer Educators	- How does Gilead propose to define *peer educators*?
	- How does Gilead propose that *uninfected individuals*, considering or taking TRUVADA for the PrEP indication, be assigned to a peer educator?
Vouchers	- Propose free condoms
Subsidized HIV-1 testing	- How does Gilead propose to define *appropriate individuals for testing*?
Assistance for viral resistance testing in individuals who sero-convert to HIV +	- How does Gilead propose that *uninfected individuals* access such a service?
Reminder Opt-In Service	- DRISK and DAVP have a number of questions about the proposed *Reminder Opt-In Service* that will be submitted in Interim Comments to the applicant.
Education materials for a clinic setting	- How does Gilead define these educational materials?
CDC Interim Guidance on HIV	- How does Gilead propose to educate heterosexual discordant couples who seek a CDC Interim Guidance? (To-date, CDC Interim

PrEP for MSM Guidance only issued for MSM)

Questions and Considerations for the ROC

The DRISK and DAVP request that the ROC consider and respond to the following questions:

1. Does the ROC concur with DRISK and DAVP's revised proposed Goals for a proposed REMS for TRUVADA for the PrEP indication?

   If not, what revisions/considerations does ROC recommend?

2. The DRISK and DAVP agree that the REMS should only address TRUVADA for the proposed PrEP indication as discussed at the Regulatory Briefing and the Center Director Briefing.

   Does the ROC concur with this position?

3. The DRISK and DAVP are aligned with recommending that the communication plan be revised to focus on outreach to key professional organizations that target likely prescribers of TRUVADA® for the PrEP indication. Both divisions are also aligned with recommending that all proposed communication plan materials focused on prescriber education and training and *uninfected individual's* education about the risks of TRUVADA for the PrEP indication appear under the ETASU, Prescriber Training and Education.

   Does the ROC concur with these revisions? If not, what alternative revisions does the ROC recommend?

4. The applicant proposed a number of REMS Elements. The DRISK and DAVP are aligned with proposing that the additional materials/services targeted to *uninfected individuals* considering or taking TRUVADA for the PrEP indication be deleted from the proposed REMS materials. Both divisions are also aligned with a proposed REMS for TRUVADA for the PrEP indication as a voluntary risk mitigation program.

   Does the ROC agree with these recommendations and deletion of the additional proposed materials/services from the proposed REMS for TRUVADA for the PrEP indication (See **Table 2.)**?

Please consider that DRISK needs to complete Interim Comments to the proposed REMS for TRUVADA for the PrEP indication to be sent by the DAVP to Gilead.

The DRISK and the DAVP need adequate time to review the applicant's responses and allow for Agency clearance.

ATTACHMENTS

Initial REMS Approval: xx/xx/2012

Supplemental NDA 21752

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)

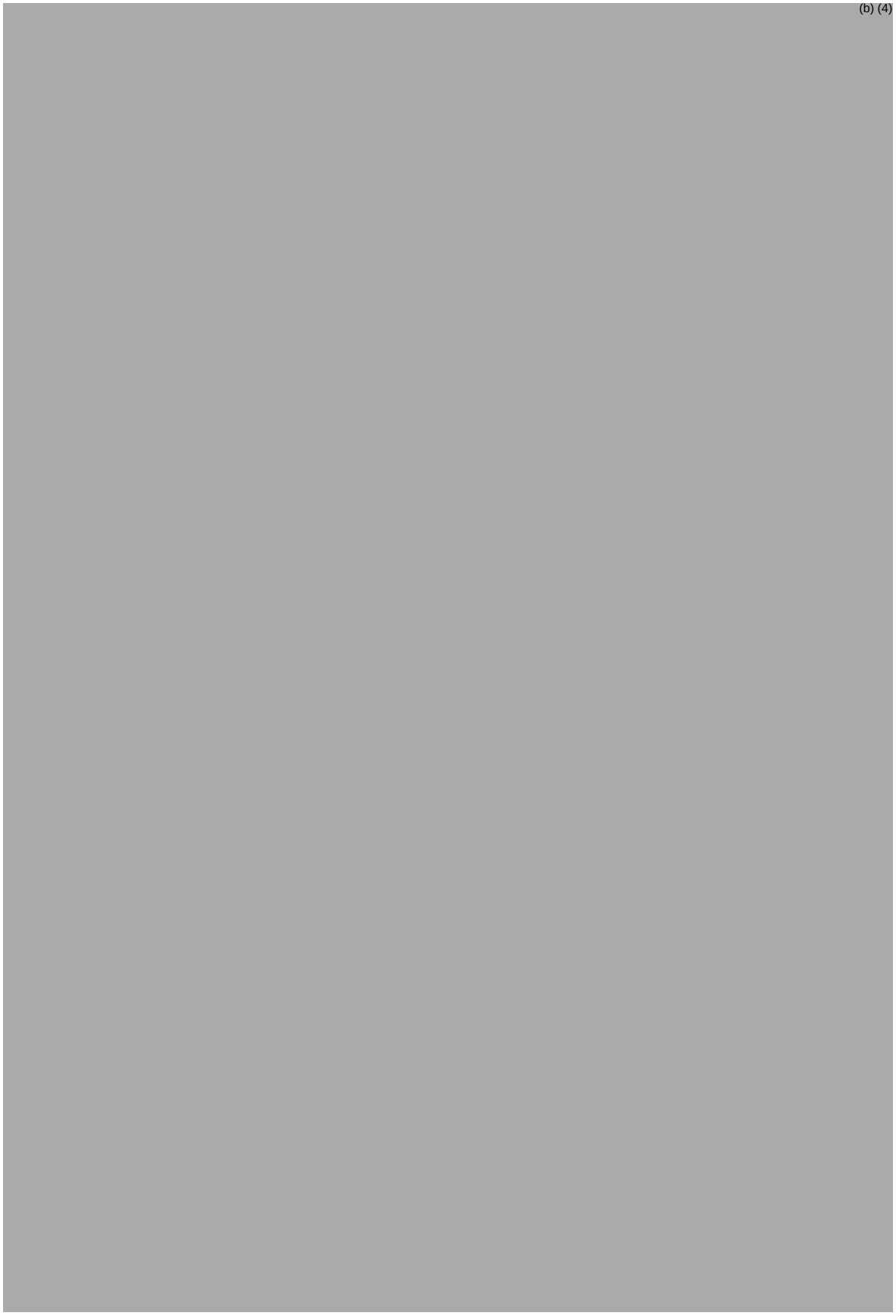
Nucleoside Analog Human Immunodeficiency Virus-1 Reverse Transcriptase Inhibitors

Gilead Sciences, Inc.

333 Lakeside Drive

Foster City, CA 94404

RISK EVALUATION AND MITIGATION STRATEGY (REMS)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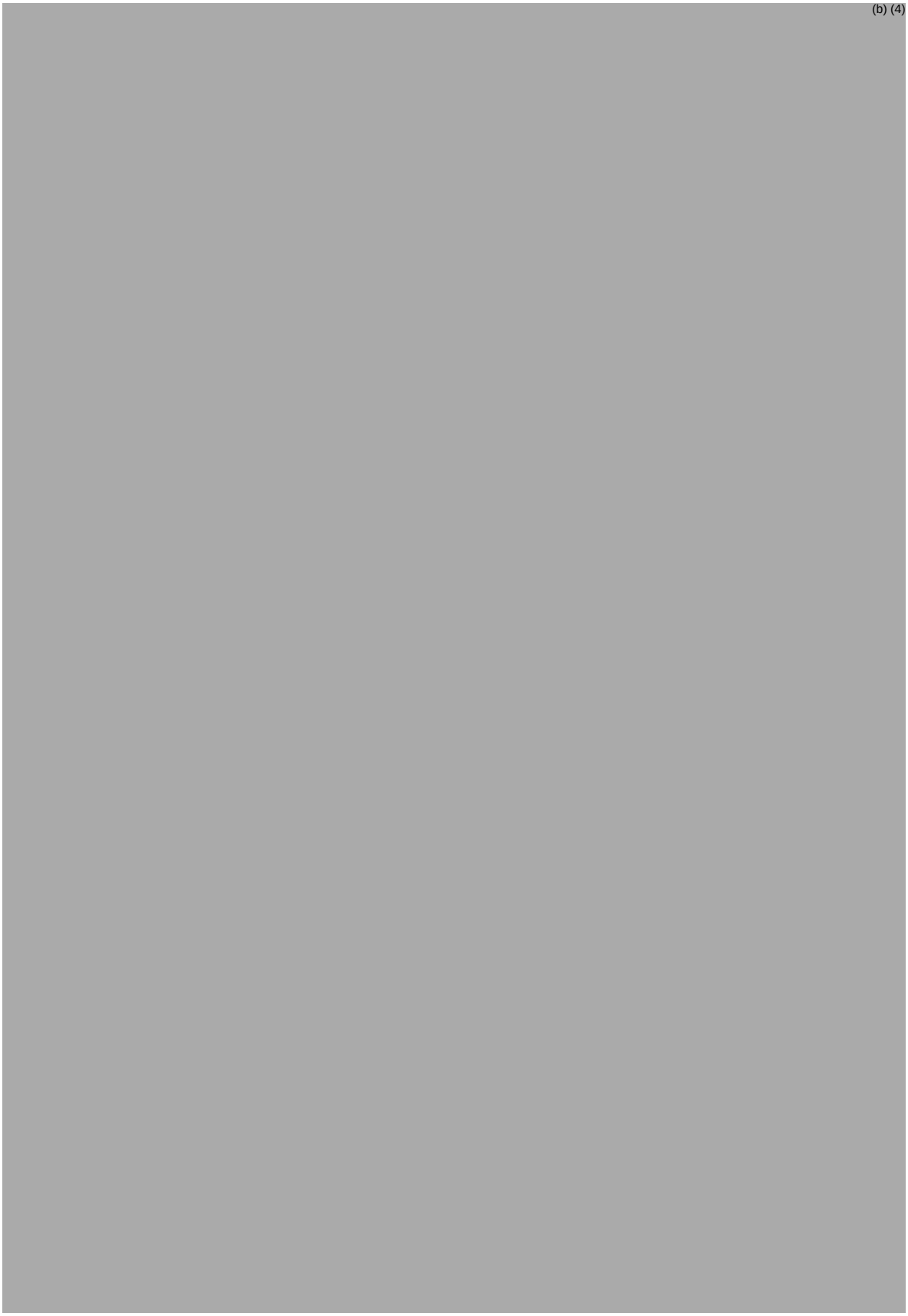
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D. Timetable for Submission of Assessments

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.

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

/s/

CAROLYN L YANCEY
04/12/2012
sNDA 021752 Interim Comments, Set 1, TURVADA for a PrEP Indication

CLAUDIA B MANZO
04/13/2012
concur