

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207561Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 29, 2015

To: Debra Birnkrant
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jessica Fox, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 207561

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On November 5, 2014, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 207561 for GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets. The Applicant proposes this new fixed dose combination tablet for the following indication: as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of GENVOYA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on November 13, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets.

2 MATERIAL REVIEWED

- Draft GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets PPI received on November 5, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 1, 2015 and further revised on October 15, 2015.
- Draft GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets Prescribing Information (PI) received on November 5, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 1, 2015 and further revised on October 15, 2015.
- Approved STRIBILD comparator labeling dated July 28, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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

/s/

SHARON R MILLS
10/29/2015

JESSICA M FOX
10/29/2015

BARBARA A FULLER
10/29/2015

LASHAWN M GRIFFITHS
10/30/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 30, 2015

To: Stacey Min, Regulatory Project Manager
Division of Antiviral Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 207561 –GENVOYA (elvitegravir, cobicistat, emtricitabine,
tenofovir alafenamide) tablets, for oral use

As requested in the Division of Antiviral Products' (DAVP) consult dated November 13, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the GENVOYA prescribing information, patient labeling, and carton/container labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information sent via email on October 19, 2015, and has no comments at this time.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling on October 30, 2015.

OPDP reviewed the carton/container labeling received in the EDR on October 9, 2015, and has no comments at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or Jessica.Fox@fda.hhs.gov.

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

/s/

JESSICA M FOX
10/30/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 207561
Product Name: GENVOYA[®] (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) 150/150/200/10 mg fixed-dose combination tablet

PMR Description: Conduct your deferred pediatric study in HIV-infected patients 6 years to less than 12 years to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate doses of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide given in combination. At least some of the safety data must be derived from dosing as the GENVOYA[®] fixed dose combination (duration and number of subjects on GENVOYA[®] to be agreed upon with the Agency).

PMR Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>09/30/2017</u>
	Final Report Submission:	<u>03/31/2018</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The drug is ready for approval in adults and pediatric patients 12 years of age or older and studies in younger pediatric patients are not complete.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the deferred study is to determine the PK profile of GENVOYA's component drugs in pediatric patients 6 to less than 12 years of age, confirm the dose that results in exposure similar to that found to be safe and effective in adult patients, and provide safety information in this pediatric age group. An assessment of antiviral activity will be performed to further support extrapolation of efficacy from the adult clinical trials. At least some of the safety data must be derived from dosing as the GENVOYA fixed dose combination (duration and number of subjects on GENVOYA to be agreed upon with the Agency).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This open-label, single-arm study will be conducted in HIV-infected patients 6 years to less than 12 years to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate doses of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide given in combination.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- X Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 207561
Product Name: GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide)
150/150/200/10 mg fixed-dose combination tablet

PMC Description: Submit the long-term safety and antiviral activity data for Study GS-US-292-0106. Include data and analyses for the entire study population through Week 48 and for all subjects enrolled in the extension phase through 96 weeks of GENVOYA® dosing.

PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>09/30/2018</u>
	Final Report Submission:	<u>03/31/2019</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The study data requested represents long-term, follow-up data that will support the safety of dosing GENVOYA for longer than 24 months (the duration of therapy included in the NDA submission). Because HIV requires continuous treatment, it is important to characterize the durability of treatment response and/or delayed adverse effects to inform treatment guidelines and clinical practice.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See above.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The long-term safety and antiviral activity data for Study GS-US-292-0106 is being collected as the study is continuing through 96 weeks of dosing. After Week 48 of dosing, subjects will be given the option to enroll in a treatment extension phase. We are requesting data and analyses for the entire study population through Week 48 and for all subjects enrolled in the extension phase through 96 weeks of GENVOYA dosing.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

X Other

Long-term extension phase data from ongoing clinical trial

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

MYUNG JOO P HONG
10/28/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: June 3, 2015

TO: Patricia Hong, Regulatory Health Project Manager
William Tauber, M. D. Medical Officer
Division of Anti-Viral Drug Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207561

APPLICANT: Gilead Sciences, Inc.

DRUG: Genvoya {elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
(E/C/E/TAF) fixed-dose combination tablet}

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Treatment of (b) (4) HIV-1 in adults and pediatric patients
CONSULTATION REQUEST DATE: December 17, 2014
DIVISION ACTION GOAL DATE: November 5, 2015
PDUFA DATE: November 5, 2015
INSPECTION SUMMARY DUE DATE: October 5, 2015

I. BACKGROUND:

The sponsor, Gilead Sciences Inc., submitted NDA 207561 for elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) fixed-dose combination single tablet for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. The proposed proprietary name under review is GENVOYA. The clinical studies supporting this program were conducted under IND 111007: Study GS-US-292-0104 and GS-US-292-0111

Investigational Drug

E/C/F/TDF (150/150/200/300mg) tablet has been approved in the United States by the FDA and is an alternative regimen approved by FDA for the treatment of HIV-1 infection in treatment naïve adults and the first approved single treatment regimen (STR) that combines an integrase strand transfer inhibitor (INSTI) with an nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone into a once-daily tablet.

Gilead Sciences' investigational tenofovir prodrug, tenofovir alafenamide (TAF), has a unique metabolism that provides enhanced lymphatic delivery of tenofovir, resulting in higher intracellular levels of the active phosphorylated moiety tenofovir-diphosphate and lower circulating levels of tenofovir. These features have the potential to improve on the efficacy and long-term safety profile of tenofovir disoproxil fumarate (TDF) which is characterized by higher systemic exposures of tenofovir and lower intracellular levels of TFV-DP, and is associated with nephrotoxicity and decreased bone mineral density.

The sponsor submitted a new formulation for approval of STR tablet, a once-daily STR fixed drug combination may provide an improved safety profile compared to other currently approved antiretrovirals for the treatment of HIV, and it may have a reduced frequency of virologic failure in HIV-infected adult and children 12 to 18 years of age.

The Applicant sponsored two pivotal clinical studies in support of the application:

1. **Study GS-US-292-0104:** “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/TenofovirAlafenamide versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults” and
2. **Study GS-US-292-0111:** “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/TenofovirAlafenamide versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults”.

The protocols for the two studies are essentially the similar; therefore a description of key design features from Protocol GS-US-292-0104 is presented as follows:

Protocol GS-US-292-0104 was a phase III, randomized, double-blind, multicenter, active-controlled, study to assess the safety and efficacy of a regimen containing a STR tablet of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) versus a STR tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) in HIV-

1infected, antiretroviral treatment naïve adults.

Subjects were randomized in a 1:1 ratio to one of the following two treatment arms:

Treatment Arm 1: STR of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (E/C/F/TAF) QD + placebo to match STR of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (E/C/F/TDF) QD.

Treatment Arm 2: STR of elvitegravir 150 mg/cobicistat150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (E/C/F/TDF) QD + placebo to match STR of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (E/C/F/TAF) QD.

Randomization was stratified by HIV-1 RNA level and CD4 count at screening. For all eligible subjects, HIV-1 genotype was analyzed at Screening. All other required tests, adverse events, laboratory analyses, HIV-1 RNA, and CD4 counts were performed at the Screening, Baseline, and all subsequent visits.

The primary objective of study was to evaluate the efficacy of a single-tablet regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) versus a STR containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) in HIV-1 positive, antiretroviral treatment naïve adult subjects as determined by the achievement of HIV-1 RNA <50 copies/mL at Week 48.

The secondary objectives were: 1) to determine the safety of the two treatment regimens as determined by the percent change from baseline in hip bone mineral density at Week 48, and 2) to determine the safety of the two treatment regimens as determined by the change from baseline in serum creatinine at Week 48.

The review division requested inspection of eight clinical investigators noted above because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average submitted to these original NDAs (two trials), 2) the selection was also a mindful of sites that participated in both pivotal studies as well as participating in the switch study, and 3) the need to determine if sites conducted the trials ethically and were in compliance with GCP regulation and local requirements. It is for these reasons that it is critical that international sites were included in the inspection.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Gordon Crofoot, M.D. 3701 Kirby Drive, Suite 1230 Houston, TX 77098 Site #2475	GS-US-292-0104 Number of subjects: 29	2/24-27/2015	NAI
Ploenchan Chetchotisakd, M.D. Khon Kaen University Srinagarind Hospital 123 Mitraparp Rd Khon Kaen, 40002 Thailand Site #4127	GS-US-292-0104 Number of subjects: 44	3/23-27/2015	VAI
Armin, Reiger, M.D. Wahringer Gurtel 18-20 Dermatologie Wien, Wien, 10090 Austria Site #4142	GS-US-292-0104 Number of subjects: 22	4/5-9/2015	Pending (preliminary classification NAI)
Daniel P. Podzamczar, M.D. Servicio de Enfermedades Infecciosas, Unidad de VIH Hospital Universitari de Bellvitge C/feixa Llarga s/n Hospitalet de Llobregat, 08907 Barcelona, Spain Site #2511	GS-US-292-0104 Number of subjects: 28 subjects	4/13-17/2015	Pending (preliminary classification NAI)
Cynthia Brinson, M.D. Central Texas Clinical Research 900 East 30 th Street Austin, TX 78805 Site #1624	GS-US-292-0111 Number of subjects 25	3/6-12/2015	NAI
Paul Benson, M.D. Be Well Medical CTR 1964 W.11 Mile Rd. Berkley, MI 48072 Site #1236	GS-US-292-0111 Number of subjects 18	1/26-2/12/2015	VAI

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Melanie Thompson, M.D. AIDS Research Consortium of Atlanta Inc. 440 Ralph McGill Boulevard NE Atlanta, GA 30312 Site# 0255	GS-US-292-0111 Number of subjects 29	2/4-13/2015	NAI
Rachel E.I. Koenig, M.D. Dominicano de Estudio Virologicos IDEV Dr. Pineyro # 211, Zona Universitaria Santo Domingo, DR Site#986	GS-US-292-0111 Number of subjects 65	4/13-17/2015	Pending (preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data found unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

**1. Gordon Crofoot, M.D.
Houston, TX 77098**

- a. What Was Inspected:** At this site, a total of 34 subjects were screened, one subject was reported as a screen failure, and 33 subjects were randomized into the study; four subjects were transferred to another site. None of the 29 subjects completed the study; the study is still ongoing. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for eight subjects were reviewed and compared to data listings. The review included drug accountability records, drug dispensing records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for eight subjects verified eligibility criteria, protocol deviations, and prohibited medications and were compared to case report forms and data listings including primary efficacy endpoints and adverse events listings.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Crofoot. Although no FDA 483 was issued to the clinical investigator, our FDA investigator discussed the minor protocol deviations such as out

of window study visits and one subject's non-compliance in taking study medications with food. The clinical investigator agreed with observations as minor protocol deviations. There were no unreported deaths and no evidence of under-reporting of adverse events. There were time limitations to the inspection.

- c. **Assessment of Data Integrity:** Although minor deviations were noted at this site,, they are unlikely to have a significant impact on data integrity or the efficacy results. The data generated by this site are considered reliable and appear acceptable in support of the pending applications.

2. **Ploenchen Chetchotisakd, M.D.** **Khon Kaen, Thailand 40002**

- a. **What Was Inspected:** At this site a total of 51 subjects were screened, seven subjects were reported as screen failures, 44 subjects were randomized into the study, and 41 subject completed the study; one subject was taken off the study drug but continued follow-up visits for monitoring purposes and one subject discontinued due going to jail. At the time of inspection all subjects completed Week 48. Review of the Informed Consent Documents, for the majority of subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for eight subjects were reviewed. The medical records/source documents for enrolled subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, financial disclosures, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/primary and secondary endpoints and adverse events reporting to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. **General Observations/Commentary:** At the conclusion of the inspection, a one-item Form FDA 483 was issued to Dr. Chetchotisakd. Our investigator presented and discussed the inspectional observation with the clinical investigator. The discussion included the failure to follow the protocol by enrolling Subject #4673 into the study prior to obtaining genetic material in order to show sensitivity to EVG, and Subject #4700 although genetic testing revealed possible resistance to tenofovir. **This subject was** later withdrawn from the study at the sponsor's request, but continued to be monitored at follow-up visits.

The clinical investigator acknowledged the inspectional observations in a written response dated April 10, 2015 in which he agreed with the observations and provided adequate explanations to include implementation of corrective actions to prevent the recurrence of the inspectional findings. OSI finds his response acceptable/adequate.

In general, the medical records reviewed were found to be in order, organized, and the data verifiable. There was no evidence of under-reporting of adverse events to the sponsor or the agency. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** Although minor regulatory deviations were noted at this site, the findings appear to be isolated and unlikely to impact the outcome of the study. The data in support of the clinical efficacy and safety at this site are considered reliable and may be used in support of the pending applications.

3. Armin Reiger, M.D.
Wien Wien, 1090 Austria

- a. **What Was Inspected:** At this site, a total of 22 subjects were screened, and 22 subjects were randomized into the study. None of the subjects completed the study; the study is still ongoing. One subject was discontinued at Week 48. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for six subjects were reviewed. The review included primary/secondary endpoints, drug accountability records, vital signs, IRB records, and inclusion/exclusion criteria. The use of concomitant medications and adverse event reporting were verified for 22 subjects. Source documents were compared to data listings for primary efficacy endpoints. In addition, the field investigator found late reporting of one adverse event, few subjects did not return back study bottles, and dexa scans for certain subjects were performed out-of-window.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Reiger. However, the above minor deficiencies were discussed with the clinical investigator who understood the deviations. There were known time limitations to the inspection due to the need for translation. There were no unreported deaths and no evidence of under-reporting of adverse events at this site.
- c. **Assessment of Data Integrity:** Although minor deviations were noted at this site, the findings appear to be isolated instances, and it is unlikely that these findings would significantly impact the outcome of the study. Overall, the data submitted in support of the clinical efficacy and safety is considered reliable and may be used in support of the pending applications.

4. Daniel Podzamczar, M.D.
Barcelona, Spain 28041

- a. **What Was Inspected:** At this site, 31 subjects were screened, three subjects were reported as screen failures, 28 subjects were enrolled, and none completed the study; study is still ongoing. One subject discontinued after Week 48. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for six subjects enrolled in the study were reviewed. For an additional five subjects, the review included adverse event reporting and

concomitant medications. The records for the six subjects compared source documents to electronic case report forms and to data listings including primary efficacy endpoints and adverse event reporting. In addition, the review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, and sponsor correspondence.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Podazamczer. However, minor deviations were discussed with the clinical investigator which included the failure to report heat sensation after drug administration, the use of concomitant medication (Nolotil), and the performance of dexta scan on multiple subjects after the first dose. In general, the medical records were found to be in order, organized, and the data verifiable. There was no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** Although minor deviations were noted at this site, overall, the data generated in support of the clinical efficacy and safety at Dr. Podazamczer's site are considered reliable and may be used in support of the pending application.

**5. Cynthia Brinson M.D.
Austin, TX 78705**

- a. What was inspected:** At this site, a total of 27 subjects were screened, and 29 subjects were randomized into the study (two subjects were transferred to this site). None of the subjects completed the study; the study is still ongoing. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for ten subjects enrolled were reviewed. The review included drug accountability records, vital signs, IRB files, primary efficacy endpoints, inclusion/exclusion criteria, study procedures, randomization, financial disclosures monitoring procedures, and use of concomitant medications, and sponsor correspondence. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events. No deficiencies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Brinson. However, the field investigator discussed with the clinical investigator the enrollment of one subject based on the condition presented at the time of inclusion, but later the subject was hospitalized for pneumonia and was given prohibited medication (iv solumedrol and a 15 day course of oral prednisone) treatment due to the subject's medical condition. The use of antibiotics is an exclusionary criterion according to the protocol. The medical monitor reviewed the case and granted approval to continue the subject in the study due to safety reasons. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Brinson’s site is reliable and may be used in support of the pending applications.

**6. Paul A. Benson, D.O.
Berkley, MI 48072**

- a. **What was Inspected:** At this site, a total of 20 were screened, two subjects were reported as screen failures, 18 subjects were enrolled, 16 subjects completed the study, and two subjects were discontinued with the reason(s) documented. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The complete medical records/source documents for 11 subjects were reviewed. The medical records/source documents for certain subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, use of concomitant medications, and adverse events reporting. Source documents for the majority of subjects were compared to case report forms and data listings.

- b. **General Observations/Commentary:** At the conclusion of the inspection, a two-item Form FDA 483 was issued to Dr. Benson. Our investigation noted failure to adhere to the investigational plan, and (b) (4)

The violations included the following:

Protocol violation:

1. According to the protocol, “All subjects with negative or trace proteinuria at baseline who develops > 1+ proteinuria on urinalysis must have a urinalysis repeated”. Our investigator found that for at least two subjects this criterion was not met. Repeat urinalysis was not performed for Subject 221-5855 and Subject 216-5608. The clinical investigator stated a policy was implemented to rectify the error.
2. According to the protocol section 7.2 “All adverse events will be assessed by the clinical investigator or qualified designee and recorded on the adverse events section of the e-CRF”. Our investigator found at least one adverse event was not reported for the following subjects:

Subject 201-5012 experienced scattered joint pain
Subject 216-5608 experienced vomiting
Subject 294-5061 experienced lightheadedness
Subject 210-5436 experienced diarrhea

The clinical investigator acknowledged the inspectional findings in a written response dated (received by the district) February 20, 2015 in which he agreed with the observations and provided adequate explanations to include implementation of

corrective actions to prevent the recurrence of the inspectional findings. OSI finds his response acceptable/adequate.

- c. **Assessment of Data Integrity:** Although minor deviations were noted at the above site, the findings appear to be isolated instances, and it is unlikely that these findings significantly impacted the outcome of the study. Overall the data generated at this site in support of the clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

7. Melanie Thompson, M.D.
Atlanta, GA 30312

- a. **What was inspected:** At this site, a total of 35 subjects were screened, seven subjects were reported as screen failures, 28 subjects were randomized into the study, and two subjects were discontinued with the reasons documented. None of the subjects completed the study; the study is still ongoing. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 14 subjects enrolled were reviewed and compared to data listings including primary efficacy endpoints and adverse events reporting. In addition, the review included drug accountability records, vital signs, IRB files, primary efficacy endpoints, inclusion/exclusion criteria, study procedures, randomization, financial disclosures monitoring procedures, and use of concomitant medications, and the sponsor correspondence, and no discrepancies were noted.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Thompson. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Thompson's site is reliable and may be used in support of the pending applications.

8. Rachel E.I. Koeing, M.D.
Santo Domingo, DR

- a. **What was inspected:** At this site, a total of 79 subjects were screened, 14 subjects were reported as screen failures, 65 subjects were randomized into the study, and three subjects were discontinued with the reasons documented. None of the 62 subjects completed the study; the study is still ongoing. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 65 subjects enrolled were reviewed and compared to data listings including primary efficacy endpoints and adverse events

reporting. In addition, the review included drug accountability records, vital signs, IRB files, primary efficacy endpoints, inclusion/exclusion criteria, study procedures, randomization, financial disclosures, monitoring procedures, use of concomitant medications, and sponsor correspondence, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Koenig. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Koenig's site is reliable and may be used in support of the pending applications.

IV. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Eight clinical investigator sites were inspected in support of this application. The inspection of two clinical investigators listed above revealed regulatory violations. The final classification for Drs. Benson and Chetchotisakd sites are Voluntary Action Indicated (VAI); for Drs. Crofoot, Thompson and Brinson are No Action Indicated (NAI), and the pending classification for Drs. Reigers, Podzameczer, and Koenig are No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

Overall, while the above findings represent observed regulatory deficiencies, these findings are unlikely to have a significant impact on data acceptability. In OSI's discussion with the review team in DAVP, DAVP noted that the above regulatory deficiencies were noncritical, expressed no specific concerns and agreed that the data submitted from these eight sites are considered acceptable and may be used in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D. M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

/s/

ANTOINE N EL HAGE
06/05/2015

SUSAN D THOMPSON
06/05/2015

KASSA AYALEW
06/05/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 4, 2015
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 207561
Product Name and Strength: Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) Tablets, 150 mg/150 mg/200 mg/10 mg
Product Type: Multi-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Gilead Sciences, Inc.
Submission Date: November 5, 2014
OSE RCM #: 2014-2305
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Acting Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Gilead Sciences, Inc. submitted this application, NDA 207561, for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed container labels and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors. The Applicant also submitted carton labeling and container labels for the Gilead Access Program.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a multi-ingredient, single-strength tablet available as, 150 mg/150 mg/200 mg/10 mg. The tablets will be packaged in 30-count bottles, which are supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed commercial container label and the FPI.

We determined that important information is displayed clearly on the proposed commercial container label and in the Dosage and Administration section within the FPI. Our review of the carton labeling and container labels for the Gilead Access Program determined that the labels and labeling are identical to the commercial products with the exception of the added statement "Gilead Access Program." Our only recommendation is that all labels and labeling should be updated to reflect the conditionally acceptable proprietary name, Genvoya.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the labels and labeling are acceptable from a medication error perspective. We only recommend that the “TRADENAME” statement be replaced with the conditionally acceptable proprietary name, Genvoya, where applicable throughout the labels and labeling. See section 4.1, below, for our recommendations.

4.1 RECOMMENDATIONS FOR GILEAD SCIENCES, INC.

A. General Recommendation

Replace “TRADENAME” with the conditionally acceptable proprietary name, Genvoya, where applicable throughout the labels and labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Genvoya that Gilead Sciences, Inc. submitted on November 25, 2014.

Table 2. Relevant Product Information for Genvoya	
Active Ingredient	elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
Indication	Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Route of Administration	Oral
Dosage Form	Tablet
Strength	150 mg/150 mg/200 mg/10 mg
Dose and Frequency	One tablet once daily
How Supplied	Bottles of 30 tablets
Storage	Store below 30 °C (86 °F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Genvoya labels and labeling submitted by Gilead Sciences, Inc on November 5, 2014.

- Container label
- Carton labeling

G.2 Label and Labeling Images



1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

MONICA M CALDERON
03/04/2015

BRENDA V BORDERS-HEMPHILL
03/04/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 207561 BLA#	NDA Supplement #: S- N/A BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: GENVOYA Established/Proper Name: elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) Dosage Form: Fixed-dose combination tablet Strengths: 150/150/200/10 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: November 5, 2014 Date of Receipt: November 5, 2014 Date clock started after UN:		
PDUFA Goal Date: November 5, 2015		Action Goal Date (if different):
Filing Date: January 4, 2015		Date of Filing Meeting: December 15, 2014
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)			
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team				
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority			
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher			
<ul style="list-style-type: none">• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)• The product is a Qualified Infectious Disease Product (QIDP)• A Tropical Disease Priority Review Voucher was submitted• A Pediatric Rare Disease Priority Review Voucher was submitted				
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>				
<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 072177, DMF 025187, and NDA 203093 for elvitegravir; IND 101283 and NDA 203094 for cobicistat; DMF 025188 for Cobicistat on Silicon Dioxide; IND 053971 and NDAs 021896 and 021500 for emtricitabine; IND 063737 for TAF, IND 067671 and NDA 021752 for Truvada; IND 103093 and NDA 203100 for Stribild;				
(b) (4) (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			

User Fee Bundling Policy Refer to the guidance for industry, <i>Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? <i>(Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:</i>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>		<input type="checkbox"/>	<input type="checkbox"/>		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm		<input checked="" type="checkbox"/>	<input type="checkbox"/>		Viread (tenofovir) was approved for orphan designation on March 17, 2009 for treatment of

				pediatric HIV infection.
<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</p> <p>If yes, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

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

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC meeting scheduled on September 9, 2015
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Agreed iPSP dated 10/29/13 is attached
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Study GS-US-292-0106 is included in the original NDA
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary name, GENVOYA was granted by DMEPA on 12/11/14
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

2

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

3

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

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 11/13/14
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 11/13/14
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 11/13/14
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

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

Version: 10/20/2014

9

All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DBRUP consult sent 12/17/14 OSI clinical inspection sent 12/17/14 Method validation consult request sent 12/18/14
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): December 17, 2012 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Preliminary comments sent 12/14/12, meeting minutes sent 1/14/13
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): May 30, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Preliminary comments sent 5/28/14, meeting request cancelled 5/29/14. Type C meeting October 30, 2014- Preliminary comments sent 10/27/14 (meeting request cancelled 10/29/14).
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 15, 2014

BACKGROUND: On November 5, 2014, Gilead Sciences has submitted PDUFA V NME for NDA 207561, GENVOYA, a fixed dose combination tablet consisting of elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide 10 mg. Elvitegravir, cobicistat and emtricitabine are all approved as single-agent NDAs and as part of fixed-dose combination tablet. NDA 207561 is the first time tenofovir alafenamide (TAF) has been submitted for NDA review. Gilead Sciences is developing TAF in fixed-dose combination tablets for HIV (b) (4)

The proposed indication of GENVOYA is for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

This PDUFA V NME will be reviewed under a Standard clock and the goal date will be November 5, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacey Min	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Y
Division Director/Deputy	Debra Birnkrant		Y
Office Director/Deputy	John Farley		Y
Clinical	Reviewer:	William Tauber	Y
	TL:	Linda Lewis	Y
Social Scientist Review (for OTC products)	Reviewer:	n/a	
	TL:	n/a	
OTC Labeling Review (for OTC products)	Reviewer:	n/a	
	TL:	n/a	
Clinical Microbiology (for antimicrobial products)	Reviewer:	Lisa Naeger	Y
	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	Mario Sampson	Y

	TL:	Islam Younis Leslie Chinn- Acting TL	N Y
Biostatistics	Reviewer:	Thomas Hammerstrom	Y
	TL:	Greg Soon Dionne Price	Y Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Claudia Wrzesinski	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	n/a	
	TL:	n/a	
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	n/a	
	TL:	n/a	
Product Quality (CMC)	Reviewer:	Jeff Medwid - DS George Lunn- DP	Y Y
	TL:	Steve Miller	Y
Biopharmaceutics	Reviewer	Salah Hamed	Y
	TL:	Angelica Dorantes	N
Quality Microbiology	Reviewer:	Jessica Cole	
	TL:	Bryan Riley	
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Krishna Ghosh	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Rhiannon Leutner	N
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Felicia Duffy	Y
	TL:	Namoi Redd	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	
	TL:	n/a	

Bioresearch Monitoring (OSI)	Reviewer:	Tony El Hage	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	
	TL:	n/a	
Other reviewers/disciplines	Reviewer:	Sharon Mills- PLT	Y
	TL:	Barbara Fuller- PLT	N
Other attendees	Navi Bhandari- CMC PM Sharon Thoma- ORA		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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

<p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (protein/peptide products only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>New Molecular Entity (NDAs only)</p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? <p>Comments: Not a sterile product</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: Part of DP Review</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>n/a</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: John Farley, M.D., MPH</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 31, 2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

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

/s/

STACEY MIN
01/07/2015

ELIZABETH G THOMPSON
01/07/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 207561

Application Type: New NDA under “the Program”

Name of Drug/Dosage Form: GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide (E/C/F/TAF) 150/150/200/10 mg tablet

Applicant: Gilead Sciences, Inc.

Receipt Date: November 5, 2014

Goal Date: November 5, 2015

1. Regulatory History and Applicant's Main Proposals

GENVOYA is a fixed-dose combination tablet consisting of elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide 10 mg. GENVOYA is a PDUFA V NME being reviewed under “the Program”. The original NDA was submitted and received on November 5, 2014 and will be reviewed under a standard clock with a PDUFA goal date of November 5, 2015.

The proposed indication for GENVOYA is for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. GENVOYA has a prescribing information (PI) and patient PI (PPI).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 30, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *HL are longer than one-half page but if HL Boxed Warning is removed, it should be one-half page.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *All headings in HL must have horizontal lines that extend the entire width of the columns however, some headings have lines do not extend the entire width of the columns and are not centered.*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *The spacing throughout HL is not consistent. There should be no extra space between the subheading title and the content below it. Below contraindications, there is extra white space between the heading and the content.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

Selected Requirements of Prescribing Information

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**"

The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: Please remove the year.

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *Original NDA so no RMC.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A

Selected Requirements of Prescribing Information

20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Only one dosage form and presented accurately.*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

STACEY MIN
01/05/2015

ELIZABETH G THOMPSON
01/06/2015