

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203094Orig1s000**

**203094Orig2s000**

**OTHER REVIEW(S)**

## 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.

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NDA/BLA # 203094 - Original 1

Product Name:

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PMR/PMC Description: 1. Conduct a trial to evaluate pediatric pharmacokinetics (PK), safety and antiviral activity of once daily atazanavir and cobicistat (ATV/COBI) combined with a background regimen in HIV-1 infected pediatric subjects. Subjects receiving ATV/COBI should be from 3 months to less than 18 years of age. Initial evaluation of ATV/COBI exposure must be performed in an initial PK study or substudy to allow dose selection. Using doses selected based on the PK study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of ATV/COBI combined with a background regimen, assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over as least 24 weeks of dosing.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>Oct 31, 2018</u>
	Final Report Submission:	<u>Jan 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 product is ready for approval in adults.

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 study(ies) is to evaluate PK, safety, and antiviral activity of COBI coadministered with ATV in pediatric subjects from 3 months to less than 18 years of age and provide a pediatric dosing recommendation.

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.

Age group: 3 months to less than 18 years of age

Approval for cobicistat is for adults only. Atazanavir with ritonavir (ATV/RTV) is currently approved for pediatric patients ages 3 months to less than 18 years. The Sponsor plans to evaluate PK, safety, and antiviral activity of ATV/COBI in HIV-1 pediatric subjects 3 months to less than 18 years of age who have suppressed viremia (HIV RNA <50 copies/mL) on a stable ATV/RTV regimen.

Part A of the study will assess steady state PK of ATV when coadministered with RTV followed by COBI. Following confirmation of acceptable ATV PK with COBI, Part B of the study will enroll additional subjects to assess long-term safety and antiviral activity of ATV/COBI plus background regimen for 48 weeks.

The sponsor plans to develop an age-appropriate formulation of COBI.

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)  
Antiviral efficacy
- 

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

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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

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**PMR/PMC Development Coordinator:**

- 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.*

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(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.

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NDA/BLA #: 203094 Original 1  
Product Name: Cobicistat

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PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2015</u>
	Study/Trial Completion:	<u>04/2016</u>
	Final Report Submission:	<u>12/2016</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 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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin is the potential for increased statin exposures which could result in adverse effects such as myopathy, including rhabdomyolysis.

In addition to atorvastatin, a second proposed postmarketing trial will evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1 and cobicistat inhibits BCRP, it is not known whether the magnitude or direction of change in statin exposure when atazanavir is coadministered with ritonavir versus cobicistat is similar.

During the review process, it was determined that the existing recommended maximum daily dose of atorvastatin 20 mg/day and rosuvastatin 10 mg/day could not be extrapolated from the darunavir and atazanavir U.S. prescribing information, respectively, to the cobicistat U.S. prescribing information because the interaction with statins is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the predicted potential inhibition effects of cobicistat 150 mg combined with atazanavir 300 mg once daily results in clinically relevant changes in atorvastatin exposure. The currently available pharmacokinetic data does not provide information on the appropriate recommended maximum daily dose of atorvastatin with concomitant use of cobicistat 150 mg combined with atazanavir 300 mg once daily.

The goal of the trial is to determine the magnitude and direction of change in atorvastatin exposure when coadministered with cobicistat 150 mg combined with atazanavir 300 mg once daily.

The risk associated with the predicted potential inhibition effects with cobicistat combined with atazanavir is the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of atorvastatin with concomitant use of steady state dosing of cobicistat coadministered with atazanavir (test arm) compared to the pharmacokinetics of atorvastatin by itself (reference arm).

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)

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Other

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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

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**PMR/PMC Development Coordinator:**

- 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.*

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## 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.

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NDA/BLA #: 203094 Original 1  
Product Name: Cobicistat

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PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2015</u>
	Study/Trial Completion:	<u>04/2016</u>
	Final Report Submission:	<u>12/2016</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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin is the potential for increased statin exposures which could result in adverse effects such as myopathy, including rhabdomyolysis.

In addition to rosuvastatin, a second proposed postmarketing trial will evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1 and cobicistat inhibits BCRP, it is not known whether the magnitude or direction of change in statin exposure when atazanavir is coadministered with ritonavir versus cobicistat is similar.

During the review process, it was determined that the existing recommended maximum daily dose of atorvastatin 20 mg/day and rosuvastatin 10 mg/day could not be extrapolated from the darunavir and atazanavir U.S. prescribing information, respectively, to the cobicistat U.S. prescribing information because the interaction with statins is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the predicted potential inhibition effects of cobicistat 150 mg combined with atazanavir 300 mg once daily results in clinically relevant changes in rosuvastatin exposure. The currently available pharmacokinetic data does not provide information on the appropriate recommended maximum daily dose of rosuvastatin with concomitant use of cobicistat 150 mg combined with atazanavir 300 mg once daily.

The goal of the trial is to determine the magnitude and direction of change in rosuvastatin exposure when coadministered with cobicistat 150 mg combined with atazanavir 300 mg once daily.

The risk associated with the predicted potential inhibition effects with cobicistat combined with atazanavir is the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of rosuvastatin with concomitant use of steady state dosing of cobicistat coadministered with atazanavir (test arm) compared to the pharmacokinetics of rosuvastatin by itself (reference arm).

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)

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Other

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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

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**PMR/PMC Development Coordinator:**

- 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.*

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(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.

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NDA/BLA #: 203094 Original 1  
Product Name: Cobicistat

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PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2015</u>
	Study/Trial Completion:	<u>06/2016</u>
	Final Report Submission:	<u>02/2017</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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive is the potential for increased or decreased estrogen or progestin exposures which could result in safety issues or oral contraceptive failure, respectively.

During the review process, it was determined that the existing recommendations on concomitant use of oral contraceptives could not be extrapolated from the atazanavir U.S. prescribing information to the cobicistat U.S. prescribing information because the interaction is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the potential effects of cobicistat 150 mg combined with atazanavir 300 mg once daily results in clinically relevant changes in estrogen or progestin exposure. The currently available pharmacokinetic data does not provide an answer to this issue.

The goal of the trial is to determine the magnitude and direction of change in estrogen or progestin exposure when coadministered with cobicistat 150 mg combined with atazanavir 300 mg once daily.

The risk associated with the potential effects of cobicistat combined with atazanavir on estrogen or progestin is the possibility that increased or decreased estrogen or progestin exposures could result in adverse effects such as venous thrombosis or oral contraceptive failure, respectively.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of the estrogen and progestin components with concomitant use of steady state dosing of cobicistat coadministered with atazanavir (test arm) compared to the pharmacokinetics of the estrogen and progestin components by itself (reference arm).

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)

- 
- 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

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**PMR/PMC Development Coordinator:**

- 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.*

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(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN D WINESTOCK  
09/24/2014

STANLEY AU  
09/24/2014

WILLIAM B TAUBER  
09/24/2014

## 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.

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NDA/BLA # 203094 - Original 2

Product Name:

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PMR/PMC Description: 1. Conduct a trial to evaluate pediatric pharmacokinetics (PK), safety and antiviral activity of once daily darunavir (DRV) and cobicistat (DRV/COBI) combined with a background regimen in HIV-1 infected pediatric subjects. Subjects receiving DRV/COBI should be from 3 years to less than 18 years of age. Initial evaluation of DRV/COBI exposure must be performed in an initial PK study or substudy to allow dose selection. Using doses selected based on the PK study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of DRV/COBI combined with a background regimen, assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over as least 24 weeks of dosing.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Trial Completion:	<u>Oct 31, 2018</u>
	Final Report Submission:	<u>Jan 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 product is ready for approval in adults.

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 study(ies) is to evaluate PK, safety, and antiviral activity of COBI coadministered with DRV once daily in pediatric subjects from 3 years to less than 18 years of age and provide a pediatric dosing recommendation.

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.

Age group: 3 years to less than 18 years of age

Approval for cobicistat is for adults only. Darunavir with ritonavir (DRV/RTV) is currently approved for pediatric patients ages 3 years to less than 18 years. The Sponsor plans to evaluate PK, safety, and antiviral activity of DRV/COBI in HIV-1 pediatric subjects 3 years to less than 18 years of age who have suppressed viremia (HIV RNA <50 copies/mL) on a stable DRV/RTV regimen.

Part A of the study will assess steady state PK of DRV when coadministered with RTV followed by COBI. Following confirmation of acceptable DRV PK with COBI, Part B of the study will enroll additional subjects to assess long-term safety and antiviral activity of DRV/COBI plus background regimen for 48 weeks.

The sponsor plans to develop an age-appropriate formulation of COBI.

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)  
Antiviral efficacy
- 

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

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**PMR/PMC Development Coordinator:**

- 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 #: 203094 Original 2  
Product Name: Cobicistat

---

PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2015</u>
	Study/Trial Completion:	<u>04/2016</u>
	Final Report Submission:	<u>12/2016</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 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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin is the potential for increased statin exposures which could result in adverse effects such as myopathy, including rhabdomyolysis.

In addition to atorvastatin, a second proposed postmarketing trial will evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1, it is not known whether the magnitude or direction of change in statin exposure when darunavir is coadministered with ritonavir versus cobicistat is similar.

During the review process, it was determined that the existing recommended maximum daily dose of atorvastatin 20 mg/day and rosuvastatin 10 mg/day could not be extrapolated from the darunavir and atazanavir U.S. prescribing information, respectively, to the cobicistat U.S. prescribing information because the interaction with statins is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the predicted potential inhibition effects of cobicistat 150 mg combined with darunavir 800 mg once daily results in clinically relevant changes in atorvastatin exposure. The currently available pharmacokinetic data does not provide information on the appropriate recommended maximum daily dose of atorvastatin with concomitant use of cobicistat 150 mg combined with darunavir 800 mg once daily.

The goal of the trial is to determine the magnitude and direction of change in atorvastatin exposure when coadministered with cobicistat 150 mg combined with darunavir 800 mg once daily.

The risk associated with the predicted potential inhibition effects with cobicistat combined with darunavir is the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of atorvastatin with concomitant use of steady state dosing of cobicistat coadministered with darunavir (test arm) compared to the pharmacokinetics of atorvastatin by itself (reference arm).

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)

---

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:**

- 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.*

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(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 #: 203094 Original 2  
Product Name: Cobicistat

---

PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2015</u>
	Study/Trial Completion:	<u>04/2016</u>
	Final Report Submission:	<u>12/2016</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 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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin is the potential for increased statin exposures which could result in adverse effects such as myopathy, including rhabdomyolysis.

In addition to rosuvastatin, a second proposed postmarketing trial will evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1, and cobicistat inhibits BCRP, it is not known whether the magnitude or direction of change in statin exposure when darunavir is coadministered with ritonavir versus cobicistat is similar.

During the review process, it was determined that the existing recommended maximum daily dose of atorvastatin 20 mg/day and rosuvastatin 10 mg/day could not be extrapolated from the darunavir and atazanavir U.S. prescribing information, respectively, to the cobicistat U.S. prescribing information because the interaction with statins is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the predicted potential inhibition effects of cobicistat 150 mg combined with darunavir 800 mg once daily results in clinically relevant changes in rosuvastatin exposure. The currently available pharmacokinetic data does not provide information on the appropriate recommended maximum daily dose of rosuvastatin with concomitant use of cobicistat 150 mg combined with darunavir 800 mg once daily.

The goal of the trial is to determine the magnitude and direction of change in rosuvastatin exposure when coadministered with cobicistat 150 mg combined with darunavir 800 mg once daily.

The risk associated with the predicted potential inhibition effects with cobicistat combined with darunavir is the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of rosuvastatin with concomitant use of steady state dosing of cobicistat coadministered with darunavir (test arm) compared to the pharmacokinetics of rosuvastatin by itself (reference arm).

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)

---

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

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**PMR/PMC Development Coordinator:**

- 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.*

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(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 #: 203094 Original 2  
Product Name: Cobicistat

---

PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2015</u>
	Study/Trial Completion:	<u>06/2016</u>
	Final Report Submission:	<u>02/2017</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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive is the potential for increased or decreased estrogen or progestin exposures which could result in safety issues or oral contraceptive failure, respectively.

During the review process, it was determined that the existing recommendations on concomitant use of oral contraceptives could not be extrapolated from the darunavir U.S. prescribing information to the cobicistat U.S. prescribing information because the interaction is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the potential effects of cobicistat 150 mg combined with darunavir 800 mg once daily results in clinically relevant changes in estrogen or progestin exposure. The currently available pharmacokinetic data does not provide an answer to this issue.

The goal of the trial is to determine the magnitude and direction of change in estrogen or progestin exposure when coadministered with cobicistat 150 mg combined with darunavir 800 mg once daily.

The risk associated with the potential effects of cobicistat combined with darunavir on estrogen or progestin is the possibility that increased or decreased estrogen or progestin exposures could result in adverse effects such as venous thrombosis or oral contraceptive failure, respectively.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of the estrogen and progestin components with concomitant use of steady state dosing of cobicistat coadministered with darunavir (test arm) compared to the pharmacokinetics of the estrogen and progestin components by itself (reference arm).

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)

- 
- 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:**

- 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.*

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(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN D WINESTOCK  
09/24/2014

WILLIAM B TAUBER  
09/24/2014

STANLEY AU  
09/24/2014

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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)

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**Date of This Memorandum:** September 17, 2014  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 203094  
**Product Name and Strength:** Tybost (cobicistat) Tablets, 150 mg  
**Submission Date:** September 15, 2014  
**Applicant/Sponsor Name:** Gilead Sciences  
**OSE RCM #:** 2014-762-1  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Associate Director:** Lubna Merchant, MS, PharmD

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#### 1 PURPOSE OF MEMO

Gilead Sciences has submitted a revised container label (Appendix A) for Tybost requesting to move the strength to its own separate line for consistency with an FDA comment on another product. Thus, the Division of Antiviral Products (DAVP) requested that we review the revised container label to determine if it is acceptable from a medication error perspective.

#### 2 CONCLUSIONS

The revised container label is acceptable from a medication error perspective. We have no recommendations at this time.

**APPENDIX A. LABEL SUBMITTED ON SEPTEMBER 15, 2014**

(b) (4)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MONICA M CALDERON  
09/17/2014

LUBNA A MERCHANT  
09/17/2014

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

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

**Memorandum**

**Date:** August 26, 2014

**To:** Karen Winestock, Chief Project Management Staff  
Division of Antiviral Products

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

**Subject:** NDA 203094 – Original 1 and Original 2  
TYBOST (cobicistat) Tablets, for oral use

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As requested in the Division of Antiviral Products' (DAVP) consult dated April 10, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed a Dear Health Care Provider (DHCP) letter for TYBOST.

OPDP's comments on the DHCP letter are provided below in the proposed substantially complete version of the letter obtained via Sharepoint on August 25, 2014.

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 at Jessica.Fox@fda.hhs.gov.

6 Pages of Draft Labeling have been Withheld in Full as B4  
(CCI/TS) Immediately Following this Page

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

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JESSICA M FOX  
08/26/2014

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

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

**Memorandum**

**Date:** August 18, 2014

**To:** Karen Winestock, Chief Project Management Staff  
Division of Antiviral Products

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

**Subject:** NDA 203094 – Original 1 and Original 2  
TYBOST (cobicistat) Tablets, for oral use

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As requested in the Division of Antiviral Products' (DAVP) consult dated April 10, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the TYBOST prescribing information, patient labeling, and carton and container labeling.

OPDP's comments on the prescribing information are provided below in the proposed substantially complete version of the labeling received via email from DAVP on August 1, 2014.

OPDP reviewed the carton and container labeling obtained from EDR location <\\CDSESUB1\evsprod\NDA203094\203094.enx> (dated May 15, 2014), 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 August 8, 2014.

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 at [Jessica.Fox@fda.hhs.gov](mailto:Jessica.Fox@fda.hhs.gov).

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/s/

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JESSICA M FOX  
08/18/2014

**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: August 8, 2014

To: Debra Birnkrant, MD  
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): TYBOST (cobicistat)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 203094, Original 1 and Original 2

Applicant: Gilead Sciences, Inc.

## 1 INTRODUCTION

On April 3, 2014, Gilead Sciences, Inc. submitted for the Agency's review a Complete Response (Class 2) to the Agency's Complete Response (CR) Letters dated April 26, 2013 for their Original New Drug Application (NDA) 203094 for TYBOST (cobicistat) Tablets. The CR letters dated April 26, 2013 cited deficiencies in the areas of Clinical Pharmacology, Facility Inspections, and Product Quality. For administrative purposes, the Agency has split this NDA into two originals:

- NDA 203094/Original 1- cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir in the treatment of HIV-1 infection in adults.
- NDA 203094/Original 2- cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of darunavir in the treatment of HIV-1 infection in adults.

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 April 10, 2014 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TYBOST (cobicistat) Tablets.

## 2 MATERIAL REVIEWED

- Draft TYBOST (cobicistat) Tablets PPI received on April 3, 2014, and received by DMPP and OPDP on August 1, 2014.
- Draft TYBOST (cobicistat) Tablets Prescribing Information (PI) received on April 3, 2014 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 1, 2014.
- DMPP Review of TYBOST (cobicistat) Patient Labeling (Patient Package Insert) dated March 20, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> 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 Verdana font, size 11.

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)

#### **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.

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/s/  
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SHARON R MILLS  
08/08/2014

JESSICA M FOX  
08/08/2014

BARBARA A FULLER  
08/08/2014

LASHAWN M GRIFFITHS  
08/08/2014

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**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\*\*\***

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**Date of This Review:** June 6, 2014  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 203094  
**Product Name and Strength:** Tybost (cobicistat) Tablets, 150 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Gilead Sciences  
**Submission Date:** May 15, 2014  
**OSE RCM #:** 2014-762  
**DMEPA Primary Reviewer:** Mónica Calderón, PharmD, BCPS  
**DMEPA Associate Director:** Lubna Merchant, MS, PharmD

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## 1 REASON FOR REVIEW

As part of the resubmission for NDA 203094, DAVP requested DMEPA evaluate Gilead's proposed container labels, carton labeling and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors. The Applicant also resubmitted Tybost carton labeling and container labels for the Gilead Access Program with this re-submission.

## 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.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
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 resubmitting the proposed container label and full prescribing information due to receiving a Complete Response under their original submission for NDA 203094. They are proposing a single strength (150 mg) tablet that will be packaged in a 30-count bottle, which is supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed container label and noted the label remains acceptable from a medication error perspective as per our previous review. DMEPA's prior comments with regards to discrepancies in the FPI of cobicistat and Stribild have been addressed by DAVP. This resubmission also contained carton labeling and container labels for Gilead Access Program products. These products will not be marketed in the United States, therefore, DMEPA did not review the carton labeling and container labels for the Gilead Access Program.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the resubmitted container label is acceptable and our previous concerns with the FPI have been addressed by DAVP. Therefore, we have no further recommendations.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tybost that Gilead Sciences submitted on March 26, 2014 .

<b>Table 2. Relevant Product Information for Tybost</b>	
<b>Active Ingredient</b>	cobicistat
<b>Indication</b>	To increase systemic exposures of atazanavir and darunavir (once daily dosing regimen) in the treatment of HIV-1 infection in adults.
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablet
<b>Strength</b>	150 mg
<b>Dose and Frequency</b>	150 mg once daily
<b>How Supplied</b>	30 count bottles
<b>Storage</b>	Store at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).
<b>Container Closure</b>	Child-resistant closure

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

We searched the L:Drive on May 29, 2014 using the terms, Tybost to identify reviews previously performed by DMEPA.

### **C.2 Results**

DMEPA last reviewed proposed labels and labeling by the Applicant for their original submission of NDA 203094 (OSE Review #2012-1483) dated November 15, 2012. DMEPA found the container label acceptable; however, comments were made to the Division with regard to inconsistencies in the FPI with the currently marketed product, Stribild.

(b) (4)

(b) (4)

## **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,<sup>1</sup> along with postmarket medication error data, we reviewed the following Tybost labels and labeling submitted by Gilead Sciences on March 26, 2014 and May 15, 2014.

- Container label (May 15, 2014)
- Full prescribing information (March 26, 2014)

### **G.2 Label and Labeling Images**

#### **Container Label submitted May 15, 2014**

(b) (4)



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

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MONICA M CALDERON  
06/06/2014

LUBNA A MERCHANT  
06/06/2014

MEMORANDUM

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

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DATE: July 3, 2013

TO: Debra B. Birnkrant, M.D.  
Director, Division of Antiviral Products  
Office of Antimicrobial Products

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Addendum to Review of EIR Covering NDA 203-094  
Cobicistat (GS-9350), 150 mg tablet sponsored by Gilead  
Sciences, Inc., USA

At the request of the Division of Antiviral Products (DAVP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected clinical and analytical portions of the following studies:

**GS-US-216-0115**: "A phase-I, multiple dose study to evaluate the relative bioavailability and pharmacokinetics of Darunavir when coadministered with the pharmacoenhancer GS-9350 versus Ritonavir"

**GS-US-216-0116**: "A phase-I, multiple dose study to evaluate two formulations of GS-9350 tablets and the pharmacokinetics of Elvitegravir tablets administered with GS-9350 tablets"

After evaluation of EIR and the firm's response to Form FDA-483 observations, DBGLPC reported the inspection outcome for the

above audit to DAVP on April 17, 2013, and recommended the following:

1. (b) (4) should conduct a long-term darunavir stability study (LTS) in the presence of cobicistat (b) (4). Without this (b) (4) LTS information, the accuracy of the darunavir data from study # GS-US-216-0115 cannot be assured.
- 2 (b) (4)
3. The data from clinical and other analytical portions of study GS-US-216-0115 are acceptable for your review.

On June 30, 2013, DBGLPC received (b) (4) **second response** to Form FDA-483 observation with respect to long-term stability (b) (4)

Our evaluation of the second response to Form FDA-483 observation (provided below) follows:

(b) (4)

In their response to the Form FDA-483, (b) (4) conducted and provided the data of (b) (4)

(b) (4)

In the opinion of this reviewer, (b) (4) long-term stability of darunavir in the presence of a co-administered compound are now acceptable.

**Conclusion:**

Following evaluation of (b) (4) second response, this reviewer recommends that the data from study # GS-US-216-0115 are now acceptable for your review.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

**VAI - Comprehensive Clinical Development, Tacoma, WA**  
FEI: 3002998793

**NAI - Seaview Research, Inc., Miami, FL**  
FEI: 3005611026

**VAI -**  
FEI:

**VAI -**  
FEI:

(b) (4)

CC:  
OSI/Moreno  
OSI/DBGLPC/Taylor/Dejernet  
OSI/DBGLPC/BB/Haidar/Choi/Mada  
OND/ODE4/DAVP/Olagundoye-Alawode/Birnkrant  
OCP/DCP4/Lazor/Au  
ORA/PHI-DO/Mangigian  
Draft: SRM 07/02/2013  
Edit: YMC 07/03/2013; SHH 07/03/2013  
OSI: BE6384; O:\Bioequiv\EIRCover\203094.gil.cob Addendum-1  
FACTS: (b) (4)  
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

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SRIPAL R MADA  
07/03/2013

SAM H HAIDAR  
07/03/2013

WILLIAM H TAYLOR  
07/03/2013

## 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 #: 203094  
Product Name: Cobicistat

---

PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

---

PMR/PMC Schedule Milestones: Final Protocol Submission:  
Study/Trial Completion:  
Final Report Submission:  
Other: \_\_\_\_\_



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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive is the potential for increased or decreased estrogen or progestin exposures which could result in safety issues or oral contraceptive failure, respectively.

During the review process, it was determined that the existing recommendations on concomitant use of oral contraceptives could not be extrapolated from the atazanavir U.S. prescribing information to the cobicistat U.S. prescribing information because the interaction is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the potential effects of cobicistat 150 mg combined with atazanavir 300 mg once daily results in clinically relevant changes in estrogen or progestin exposure. The currently available pharmacokinetic data does not provide an answer to this issue.

The goal of the trial is to determine the magnitude and direction of change in estrogen or progestin exposure when coadministered with cobicistat 150 mg combined with atazanavir 300 mg once daily.

The risk associated with the potential effects of cobicistat combined with atazanavir on estrogen or progestin is the possibility that increased or decreased estrogen or progestin exposures could result in adverse effects such as venous thrombosis or oral contraceptive failure, respectively.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of the estrogen and progestin components with concomitant use of steady state dosing of cobicistat coadministered with atazanavir (test arm) compared to the pharmacokinetics of the estrogen and progestin components by itself (reference arm).

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)

- 
- 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

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**PMR/PMC Development Coordinator:**

- 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.*

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STANLEY AU  
04/19/2013

KENDALL A MARCUS  
04/21/2013

## 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.

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NDA/BLA #: 203094  
Product Name: Cobicistat

---

PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosvastatin.

---

PMR/PMC Schedule Milestones: Final Protocol Submission: (b) (4)  
Study/Trial Completion: (b) (4)  
Final Report Submission: (b) (4)  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type 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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin is the potential for increased statin exposures which could result in adverse effects such as myopathy, including rhabdomyolysis.

In addition to rosuvastatin, a second proposed postmarketing trial will evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1 and cobicistat inhibits BCRP, it is not known whether the magnitude or direction of change in statin exposure when atazanavir is coadministered with ritonavir versus cobicistat is similar.

During the review process, it was determined that the existing recommended maximum daily dose of atorvastatin 20 mg/day and rosuvastatin 10 mg/day could not be extrapolated from the darunavir and atazanavir U.S. prescribing information, respectively, to the cobicistat U.S. prescribing information because the interaction with statins is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the predicted potential inhibition effects of cobicistat 150 mg combined with atazanavir 300 mg once daily results in clinically relevant changes in rosuvastatin exposure. The currently available pharmacokinetic data does not provide information on the appropriate recommended maximum daily dose of rosuvastatin with concomitant use of cobicistat 150 mg combined with atazanavir 300 mg once daily.

The goal of the trial is to determine the magnitude and direction of change in rosuvastatin exposure when coadministered with cobicistat 150 mg combined with atazanavir 300 mg once daily.

The risk associated with the predicted potential inhibition effects with cobicistat combined with atazanavir is the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of rosuvastatin with concomitant use of steady state dosing of cobicistat coadministered with atazanavir (test arm) compared to the pharmacokinetics of rosuvastatin by itself (reference arm).

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)

---

Other

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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:**

- 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.*

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/s/  
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STANLEY AU  
04/19/2013

KENDALL A MARCUS  
04/21/2013

## 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 #: 203094  
Product Name: Cobicistat

---

PMR/PMC Description: A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin.

---

PMR/PMC Schedule Milestones: Final Protocol Submission: (b) (4)  
Study/Trial Completion: (b) (4)  
Final Report Submission: (b) (4)  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type 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 theoretical concern for requesting a trial as a postmarketing requirement to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin is the potential for increased statin exposures which could result in adverse effects such as myopathy, including rhabdomyolysis.

In addition to atorvastatin, a second proposed postmarketing trial will evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1 and cobicistat inhibits BCRP, it is not known whether the magnitude or direction of change in statin exposure when atazanavir is coadministered with ritonavir versus cobicistat is similar.

During the review process, it was determined that the existing recommended maximum daily dose of atorvastatin 20 mg/day and rosuvastatin 10 mg/day could not be extrapolated from the darunavir and atazanavir U.S. prescribing information, respectively, to the cobicistat U.S. prescribing information because the interaction with statins is due to complex or unknown mechanisms of drug-drug interaction.

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 review issue is to determine whether the predicted potential inhibition effects of cobicistat 150 mg combined with atazanavir 300 mg once daily results in clinically relevant changes in atorvastatin exposure. The currently available pharmacokinetic data does not provide information on the appropriate recommended maximum daily dose of atorvastatin with concomitant use of cobicistat 150 mg combined with atazanavir 300 mg once daily.

The goal of the trial is to determine the magnitude and direction of change in atorvastatin exposure when coadministered with cobicistat 150 mg combined with atazanavir 300 mg once daily.

The risk associated with the predicted potential inhibition effects with cobicistat combined with atazanavir is the possibility that increased statin exposures could result in adverse effects such as myopathy, including rhabdomyolysis.

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 clinical trial in healthy subjects will evaluate the pharmacokinetics of atorvastatin with concomitant use of steady state dosing of cobicistat coadministered with atazanavir (test arm) compared to the pharmacokinetics of atorvastatin by itself (reference arm).

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)

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Other

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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:**

- 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.*

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/s/  
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STANLEY AU  
04/19/2013

KENDALL A MARCUS  
04/21/2013

**MEMORANDUM**

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

---

DATE: April 16, 2013

TO: Debra B. Birnkrant, M.D.  
Director, Division of Antiviral Products  
Office of Antimicrobial Products

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

Jyoti B. Patel, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-094 Cobicistat (GS-9350), 150 mg tablet from Gilead Sciences, Inc., USA

At the request of the Division of Antiviral Products (DAVP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected clinical and analytical portions of the following studies:

**GS-US-216-0115**: "A phase-I, multiple dose study to evaluate the relative bioavailability and pharmacokinetics of Darunavir when coadministered with the pharmacoenhancer GS-9350 versus Ritonavir"

**GS-US-216-0116**: "A phase-I, multiple dose study to evaluate two formulations of GS-9350 tablets and the

pharmacokinetics of Elvitegravir tablets  
administered with GS-9350 tablets"

**Clinical (GS-US-216-0115):**

The inspection of the clinical portion of the study was conducted by Maria P. Kelly-Doggett (ORA) and Stephanie A. Slater (ORA) at **Comprehensive Clinical Development (f.k.a Charles River Clinical Services, Inc.), 3615 Pacific Avenue Tacoma, WA (CCD)**. Following the inspection [REDACTED] <sup>(b) (4)</sup>, Form FDA-483 was issued (**Attachment 1**). The firm's response was received on March 15, 2013 (**Attachment 2**).

(b) (4)

[REDACTED] (b) (4)

In the opinion of this reviewer, CCD's response is adequate and this error will have no impact on study outcome.

**Clinical (GS-US-216-0116):**

The inspection of the clinical portion of the study was conducted by Craig A. Garmendia (ORA) at Seaview Research, Inc. 3898 N.W. 7<sup>th</sup> street, Miami, FL. Following the inspection [REDACTED] (b) (4), no major issues were identified and no Form FDA-483 was issued.

**Analytical (GS-US-216-0115):**

The inspection of the analytical portion was conducted by Sripal R. Mada, Ph.D. (OSI) and Stephanie C. Mangigian, RN (ORA) at [REDACTED] (b) (4)

Following the inspection [REDACTED] (b) (4), Form FDA-483 was issued (**Attachment 3**). The firm's response was received on March 25, 2013 (**Attachment 4**).

The Form FDA-483 observations, Frontage's response to Form FDA-483 and DBGLPC's evaluation follow:

[REDACTED] (b) (4)

In their response to the Form FDA-483, [REDACTED] (b) (4)

[REDACTED]

[REDACTED] initiated an additional long-term stability study of darunavir in the presence of cobicistat [REDACTED] (b) (4). The results of long-term stability for 54 days should be available after June 30, 2013.

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(b) (4)

Analytical (GS-US-216-0116):

The inspection of the analytical portion was conducted by Jyoti B. Patel, Ph.D. (OSI) and Stephanie C. Mangigian, RN (ORA) at

(b) (4)

Following the inspection (b) (4) Form FDA-483 was issued (**Attachment 10**). The firm's response was received on December 21, 2012 (**Attachment 11**).

(b) (4)

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**Conclusions:**

Following the evaluation of the inspectional findings and firm's response, the DBGLPC reviewers recommends the following:

**GS-US-216-0115:**

- (b) (4) should conduct a long-term darunavir stability study (LTS) (b) (4). Without this LTS information, the accuracy of the darunavir data from study # GS-US-216-0115 cannot be assured.

- (b) (4)

- The data from clinical and other analytical portions of study GS-US-216-0115 are acceptable for your review.

**GS-US-216-0116:**

- The data from clinical and analytical portions of study GS-US-216-0116 are acceptable for your review with the exception of analytical data for (b) (4)

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

Jyoti B. Patel, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

**VAI - Comprehensive Clinical Development, Tacoma, WA**  
FEI: 3002998793

**NAI - Seaview Research, Inc., Miami, FL**  
FEI: 3005611026

**VAI -**  
FEI:

**VAI -**  
FEI:

(b) (4)

cc:

OSI/Moreno

OSI/DBGLPC/Taylor/Dejernet

OSI/DBGLPC/BB/Haidar/Bonapace/Choi/Patel/Mada

OND/ODE4/DAVP/Olagundoye-Alawode/Birnkrant

OCP/DCP4/Lazor/Au

ORA/PHI-DO/Mangigian

ORA/SEA-DO/Kelly-Doggett/Slater

ORA/FLA-DO/Garmendia/Brunilda

Draft: SRM 04/08/2013; JBP 04/01/2013

Edit: YMC 04/10/2013; CRB 04/12/2013; WHT 04/12/2013, 04/15/2013;

SHH 04/16/2013

OSI: BE6384; O:\Bioequiv\EIRCover\203094.gil.cob

FACTS: (b) (4)

ECMS: [Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB](#)

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SRIPAL R MADA  
04/16/2013

JYOTI B PATEL  
04/16/2013

SAM H HAIDAR  
04/16/2013

WILLIAM H TAYLOR  
04/17/2013

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

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

**Memorandum**

**Date:** March 20, 2013

**To:** Abiola Olagundoye-Alawode, PharmD, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Jessica Fox, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 203094  
Cobicistat tablets, for oral use

---

As requested in DAVP's consult dated July 26, 2012, OPDP reviewed the proposed substantially complete versions of the cobicistat prescribing information (PI), patient labeling (PPI), and carton and container labeling.

OPDP's comments on the PI and carton and container labeling were provided under separate cover on March 19, 2013.

OPDP reviewed the proposed PPI sent via email by the Division of Medical Policy Programs on March 20, 2013, and has one comment, provided below.

Thank you for your consult. If you have any questions, please contact Jessica Fox at 301-796-5329 or at [Jessica.Fox@fda.hhs.gov](mailto:Jessica.Fox@fda.hhs.gov).

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/s/  
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JESSICA M FOX  
03/20/2013

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

**PATIENT LABELING REVIEW**

Date: March 19, 2013

To: Debra Birnkrant, MD  
**Director 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)**

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

Drug Name (established name): TYBOST (cobicistat)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 203-094

Applicant: Gilead Sciences, Inc.

## 1 INTRODUCTION

On June 28, 2012 Gilead Sciences, Inc. submitted for the Agency's review an Original New Drug Application (NDA) 203-904 for TYBOST (cobicistat) tablets. TYBOST (cobicistat) is a New Molecular Entity (NME) with a proposed indication as a pharmacokinetic enhancer of the HIV-1 protease inhibitors (PIs) atazanavir and darunavir (once daily) in adults. The active ingredient, cobicistat, was approved as a component of the fixed-dose combination tablet Stribild (cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil fumarate) on August 27, 2012 under NDA 203-100. On July 26, 2012, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for TYBOST (cobicistat) tablets.

This review is written in response to a request by DAVP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for TYBOST (cobicistat) tablets.

## 2 MATERIAL REVIEWED

- Draft TYBOST (cobicistat) tablets Patient Package Insert (PPI) received on July 26, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 12, 2013.
- Draft TYBOST (cobicistat) tablets Prescribing Information (PI) received on July 26, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 12, 2013.
- STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Tablets (NDA 203-100) approved PI and PPI dated August 27, 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured consistency with the STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Tablets PPI where applicable

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP 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.

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/s/  
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SHARON R MILLS  
03/20/2013

BARBARA A FULLER  
03/20/2013

LASHAWN M GRIFFITHS  
03/20/2013

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

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

## Memorandum

**Date:** March 19, 2013

**To:** Abiola Olagundoye-Alawode, PharmD, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Jessica Fox, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 203094  
Cobicistat tablets, for oral use

---

As requested in DAVP's consult dated July 26, 2012, OPDP reviewed the proposed substantially complete versions of the cobicistat prescribing information (PI), patient labeling (PPI), and carton and container labeling.

OPDP's comments on the PI are provided below in the proposed labeling sent via email by DAVP on March 12, 2013.

OPDP's comments on the PPI will follow under separate cover.

OPDP reviewed the carton and container labeling, dated June 28, 2012, accessed via the EDR location: <\\CDSESUB1\EVSPROD\NDA203094\203094.enx>, and has no comments at this time.

Thank you for your consult. If you have any questions, please contact Jessica Fox at 301-796-5329 or at [Jessica.Fox@fda.hhs.gov](mailto:Jessica.Fox@fda.hhs.gov).

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JESSICA M FOX  
03/19/2013

**M E M O R A N D U M**

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

---

**CLINICAL INSPECTION SUMMARY**

DATE: February 8, 2013

TO: Abiola Olagundoye, Pharm.D., Regulatory Health Project Manager  
Peter Miele, M.D., Medical Officer  
Division of Antiviral Drug Products

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

THROUGH: Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-094

APPLICANT: Gilead Sciences, Inc.

DRUG: cobicistat (Tybost)

NME: No

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: Pharmacokinetic enhancer of the HIV-1 protease inhibitors atazanavir and darunavir in adults

CONSULTATION REQUEST DATE: August 1, 2012

DIVISION ACTION GOAL DATE: April 28, 2013

INSPECTION SUMMARY GOAL DATE: March 15, 2013

PDUFA DATE: April 28, 2013

## **I. Background Information**

Gilead Sciences, Inc. submitted this application for the use of a single drug (one tablet) in the treatment of HIV-1 infected naïve adults as a pharmacokinetic enhancer of atazanavir or darunavir. One clinical trial was submitted in support of the application: Study GS-US-216-0114.

### **Investigational Drug**

Gilead has developed GS-9350 (cobicistat), a first-in-class pharmacoenhancer agent to be used with specific protease inhibitor drugs for the treatment of HIV-1 infection. GS-9350 is devoid of anti-HIV activity, may have less adverse biochemical effects such as lipid accumulation relative to ritonavir, and can be coformulated as a tablet with other agents that require boosting. GS-9350 is a structural analogue of ritonavir (RTV), and has been shown to be an irreversible inhibitor of CYP3A enzymes with greater specificity than RTV. GS-9350 is being developed as a pharmacoenhancer (booster) to increase the systemic levels of coadministered agents metabolized by CYP3A enzymes, specifically elvitegravir (EVG), and could be an alternative to ritonavir in combination with EVG and /or with HIV protease inhibitors.

Although cobicistat is not an NME, it is currently being reviewed as part of an application for a fixed-dose combination tablet of EVG/FTC/TDF/GS-9350 which resulted in a sustained virologic response (SVR); i.e., a substantial decrease in the presence of HIV RNA and an increase in CD4 counts. The applicant is seeking to market cobicistat as a new stand-alone agent. Safety and efficacy in support of the application are based primarily on 48-week data from GS-US 216-0114, a phase 3 trial comparing atazanavir boosted by cobicistat to traditional ritonavir-boosted atazanavir in treatment-naïve HIV-1 infected subjects.

### **Protocol GS-US-216-0114**

The objective of this study was to evaluate the efficacy of a regimen containing boosted atazanavir versus ritonavir-boosted atazanavir, each administered with emtricitabine/tenofovir disoproxil fumarate, in HIV-1 infected, antiretroviral treatment naïve adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at week 48.

The secondary objective of this study was to evaluate the efficacy, safety, and tolerability of the two treatment regimens through 96 weeks of treatment.

This protocol was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of a regimen containing a GS-9350-boosted atazanavir (ATV/GS-9350) versus ritonavir-boosted atazanavir (ATR/r) each administered with emtricitabine/tenofovir disoproxil fumarate (Truvada, FTC/TDF) in HIV-1 infected, antiretroviral treatment-naïve adults. Subjects were randomized in a 1:1 ratio to one of the following two treatment arms:

Treatment Arm 1: GS-9350 150 mg + atazanavir 300 mg + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg + Placebo to match ritonavir 100 mg QD (n =350)

Treatment Arm 2: Ritonavir 100 mg +atazanavir 300 mg +emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg + Placebo to match GS-9350 150 mg QD.

Randomization was stratified by HIV-1 RNA level (<100,000 copies/mL or >100,000 copies/mL) at screening. In brief, qualifying subjects must be adult males or females who are treatment naive with HIV-RNA levels >5,000 copies/mL at screening. Screening genotype must show sensitivity to FTC, TDF and ATV. Female subjects used adequate birth control.

The review division requested inspection of three clinical investigators, two domestic site inspections and one foreign site, for the pivotal protocol Study GS-US-236-0114. The consult to OSI states that these inspections were requested of these sites because, “The enrollment of large numbers of study subjects, significant primary efficacy results pertinent to decision-making, and to verify the quality of conduct of the study”

**II. RESULTS (by protocol/site):**

<b>Name of CI, location, and site #</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Rachel E. L. Koenig, M.D. Instituto Dominico de Estudios Virologicos (IDEV) Calle Dr. Pifeyro 211, Zona Universitaria, Santo Domingo Dominican Republic Site #0986	Protocol GS-US-216-0114 Number of Subjects 58	10/22-26/2012	Pending (Preliminary classification NAI)
Cynthia Mayer, M.D. St. Joseph’s Comprehensive Research Institute 4600 North Habana Ave., Suite 23 Tampa, FL 33614 Site # 2843	Protocol GS-US-216-0114 Number of Subjects 11	9/17-27/2012	NAI
David Parks, M.D. Central West Clinical Research, Inc. 3960 Lindell Blvd. St Louis, MO 63108 Site #1965	Protocol GS-US-216-0114 Number of Subjects 9	9/24-28/2012	NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Rachel E.L. Koenig, M.D.**  
**Santo Domingo, Dominican Republic**

**a. What Was Inspected:** At this site, 77 subjects were screened, 19 subjects were reported as screen failures, 58 subjects were randomized, and 54 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent prior to enrollment.

The medical records/source documents for 58 subjects were reviewed for primary efficacy endpoint, and a comprehensive study record was performed for a total of 20 subjects. The review included drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for 20 subjects were compared to case report forms and data listings, to include primary efficacy endpoint and adverse events.

**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, in support of the clinical efficacy and safety at Dr. Koenig's site are considered reliable and appear acceptable in support of the application.

2. **Cynthia Mayer, DO.**  
**Tampa, FL 33614**

**a. What Was Inspected:** At this site, a total of 13 were screened, and 2 subjects were reported as screen failures. Eleven (11) subjects were randomized into the study, three subjects withdrew and nine subjects are currently on the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for nine subjects enrolled were reviewed. Inspection revealed that source documents were organized and complete. The review included consent forms, drug accountability records, vital signs, laboratory results, IRB records, sponsor correspondence, prior and current medications, adverse events listings, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Cynthia Mayer. However, inspectional observations were discussed with the clinical investigator. The discussion included four subjects who exceeded the Screening window beyond the 35 day limit according to the protocol. In addition, Subjects 8031 and 8032 discarded at least three bottles of test articles preventing accurate documentation of study drug usage by the subjects. The clinical

investigator agreed with the observations and provided no specific reason(s). The above issues were discussed with the review division medical officer who agreed that the findings are insignificant and would have no impact on the acceptability of the data.

**c. Assessment of Data Integrity:** Despite the noted observations these appear to be isolated instances and it is unlikely that these errors significantly impacted the outcome of the study. Thus, the data generated at Dr. Mayer’s site in support of clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

**3. David Parks, M.D.  
St Louis, MO 63108**

**a. What Was Inspected:** At this site, a total 11 subjects were screened, and one subject was reported as a screen failure. Nine subjects were randomized into the study, one subject withdrew, and Subject 8024 missed two visits due to hospitalization for kidney stones and was discontinued. Eight subjects are currently on the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed. An audit of all subjects’ records was conducted. Inspection revealed the source documents were organized and complete. The review included informed consent, primary/secondary endpoints, drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Parks. However, inspectional observations were discussed with the clinical investigator and included subjects’ scheduled visits were outside the targeted window (2 days late) for two subjects. In addition, Subject 8034 signed the revised consent form at a later date on his next visit. The clinical investigator agreed with the observations and stated that sometimes it is hard to schedule visits within the schedule visits due to subjects’ limited availability. 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, in support of the clinical efficacy and safety at Dr. Parks’ site are considered reliable and appear acceptable in support of the pending application.

### **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Three clinical investigator sites were inspected in support of this application. The inspection of Drs. Mayer and Parks revealed no regulatory violations, and the classifications for these inspections are noted as No Action Indicated (NAI). The interim classification for Dr. Koenig's site is classified as pending (NAI), and the final classification will be determined upon review of the establishment inspection report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. While minor observations were noted during the inspections, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect of the findings noted above on overall data integrity to be significant. Overall, the data submitted from these three sites are considered acceptable in support of the pending application.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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ANTOINE N EL HAGE  
02/12/2013

SUSAN D THOMPSON  
02/12/2013

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

**Label, Labeling and Packaging Review**

Date: November 15, 2012

Reviewer: Morgan Walker, Pharm.D., M.B.A.  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, Pharm.D., BCPS  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh.  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Tybost (Cobicistat) 150 mg Tablets

Application Type/Number: NDA 203094

Applicant: Gilead Sciences

OSE RCM #: 2012-1483

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

## Contents

1	Introduction.....	1
1.1	Product Information .....	1
2	Methods and Materials Reviewed.....	1
2.1	Labels and Labeling .....	1
2.2	Previously Completed Reviews .....	2
3	Assessment of Medication Error Potential of the Proposed Product.....	2
3.1	Insert Labeling Risk Assessment .....	2
4	Conclusions.....	2
5	Recommendations.....	2
	Appendices.....	4

## **1 INTRODUCTION**

This review evaluates the proposed container label and insert labeling for Tybost (Cobicistat) Tablets, 150 mg, for areas of vulnerability that could lead to medication errors.

### **1.1 PRODUCT INFORMATION**

The following product information is provided in the June 28, 2012 submission.

- Proprietary Name: Tybost
- Established Name: Cobicistat
- Indication of Use: Pharmacokinetic enhancer of the HIV-1 protease inhibitors atazanavir and darunavir in adults
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 150 mg
- Dose: One tablet once daily with food with either atazanavir 300 mg once daily or darunavir 800 mg once daily
- How Supplied: 30-count bottles
- Storage: Store at 25°C (77°F), excursions permitted to 15 to 30°C (59 to 86°F) (see USP Controlled Room Temperature).

## **2 METHODS AND MATERIALS REVIEWED**

DMEPA reviewed the Tybost label and package insert labeling submitted by the Applicant.

### **2.1 LABELS AND LABELING**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted June 28, 2012 (Appendix A)
- Insert Labeling submitted June 28, 2012

It should be noted that this submission also contained carton labeling and container labels for the Gilead Access Program products. These products will not be marketed in the United States, therefore, DMEPA did not review the carton labeling and container labels for the Gilead Access Program.

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

## 2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously completed proprietary name reviews in OSE Review #2011-2499 for Tybost (Cobicistat) under IND 101283 and # 2012-1481 for Tybost (Cobicistat) under NDA 203094. The proprietary name, Tybost, was found acceptable in both reviews.

## 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

A review of Cobicistat's proposed insert labeling identified an inconsistency with the currently marketed product, Stribild. Stribild is a currently marketed product that contains Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate. Elvitegravir is the integrase inhibitor component of the product Stribild. In Section 12.4 Microbiology of the Stribild insert labeling, it states the following:

*“Cobicistat: Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A4 subfamily. Inhibition of the CYP3A-mediated metabolism by Cobicistat enhances the systemic exposure of CYP3A4 substrates, such as Elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.”*

(b) (4)

## 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label is acceptable from a medication error perspective. However, a review of the insert labeling identified an inconsistency with the currently marketed product, Stribild. We have provided comments for DAVP's consideration in Section 4.1 below.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

### 4.1 COMMENTS TO THE DIVISION OF ANTIVIRAL PRODUCTS

A review of Cobicistat's proposed insert labeling identified an inconsistency with the currently marketed product, Stribild. Stribild is a currently marketed product that contains Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate. Elvitegravir is the integrase inhibitor component of the product Stribild. In Section 12.4 Microbiology of the Stribild insert labeling, it states the following:

*“Cobicistat: Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A4 subfamily. Inhibition of the CYP3A-mediated metabolism by Cobicistat enhances the systemic exposure of CYP3A4 substrates, such as*

Elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.”

(b) (4)

(b) (4) DMEPA

defers to DAVP to determine whether it is appropriate to include information regarding Elvitegravir in the insert labeling for Cobicistat.

**APPENDICES**

**APPENDIX A: CONTAINER LABEL**



(b) (4)

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/s/  
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MORGAN A WALKER  
11/15/2012

IRENE Z CHAN  
11/15/2012

CAROL A HOLQUIST  
11/16/2012

M E M O R A N D U M

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

---

DATE: October 25, 2012

TO: Associate Director  
International Operations Drug Group  
Division of Foreign Field Investigations

Director, Investigations Branch  
Seattle District Office  
22201 23<sup>rd</sup> Dr. SE  
Bothell, WA 98021

Director, Investigations Branch  
Philadelphia District Office  
U.S. Customhouse Room 900  
2<sup>nd</sup> & Chestnut Streets  
Philadelphia, PA 19106

Director, Investigations Branch  
Florida District Office  
555 Winderley Place, Suite 200  
Maitland, FL 32751

From: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2013, High Priority User Fee NDA, For-Cause, Pre-Approval Data Validation Inspection Bioresearch Monitoring, Human Drugs, CP 7348.001**

RE: NDA 203-094  
DRUG: Cobicistat (GS-9350), 150 mg tablet  
SPONSOR: Gilead Sciences, Inc.  
Foster City, CA 94404, U.S.A.  
Contact: Christophe Beraud, Ph.D.  
Tel: 650-574-3000  
Fax: 650-522-5489

This memo requests that you arrange for inspections of the clinical and analytical portions of the following two bioequivalence studies (GS-US-216-0115 and GS-US-216-0116). **A DBGC scientist with specialized knowledge may participate in the inspection of analytical sites to provide scientific and technical expertise. Please contact DBGC point of contact (POC) upon receipt of this assignment to arrange scheduling of analytical inspections. These inspections should be completed before January 31, 2013.** Following identification of the investigator, background materials will be forwarded directly. Please contact the DBGC point of contact for background materials.

**Do not identify the application, the studies to be inspected, drug names, or the study investigator prior to the start of the inspection. The information will be provided to the sites at the inspection opening meeting. Please note that these inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, and not under CP 7348.811 (Clinical Investigators).**

**At the completion of the inspection, please send a scanned copy of the completed sections A & B of this memo to Dr. Sam Haidar, and the DBGLPC POC listed at the end of this memo.**

**Study Number:** GS-US-216-0115  
**Study Title:** "A phase-I, multiple dose study to evaluate the relative bioavailability and pharmacokinetics of Darunavir when co-administered with the pharmacoenhancer GS-9350 versus Ritonavir"

**Clinical Site:** Comprehensive Clinical Development  
(f.k.a. Charles River Clinical Services, Inc.)  
3615 Pacific Avenue  
Tacoma, WA 98418  
TEL: (253)593-5304  
FAX: (253)593-5181

**Investigator:** Nicole A. Grunenber, M.D.

**Study Number:** GS-US-216-0116  
**Study Title:** "A phase-I, multiple dose study to evaluate two formulations of GS-9350 tablets and the pharmacokinetics of Elvitegravir tablets administered with GS-9350 tablets"

**Clinical Site:** Seaview Research, Inc.  
3898 N.W. 7th street  
Miami, FL 33126  
TEL: (305) 649-6556 ext 414  
FAX: (305) 649-9019

**Investigator:** Stuart Harris, M.D., Ph.D.

**Please confirm documented informed consent for 100% of subjects enrolled at the each site. The subject records in the NDA submission should be compared to the original documents at the firm. Include a description of your findings in the EIR.**

#### **SECTION A**

**RESERVE SAMPLES:** Because these are bioequivalence studies, subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucml20265.htm>). Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.**
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing**

of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.

- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:

Benjamin Westenberger, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Courthouse and Customhouse Bldg.  
1114 Market Street, Room 1002  
St. Louis, MO 63101  
TEL: (314) 539-2135

#### SECTION B

##### **Data Audit Checklist:**

- Evidence of under-reporting of AEs identified? \_\_\_\_\_
- Evidence of inaccuracy in electronic data capture? \_\_\_\_\_
- Presence of 100% of signed and dated informed consent forms: \_\_\_\_\_
- Reports for the subjects audited: \_\_\_\_\_
- Number of subjects screened at the site: \_\_\_\_\_
- Number of subjects enrolled at the site: \_\_\_\_\_
- Number of subjects completing the study: \_\_\_\_\_
- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms: \_\_\_\_\_
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol: \_\_\_\_\_
- Number of subject records reviewed during the inspection: \_\_\_\_\_

- SOPs were followed during study conduct:\_\_\_\_\_
  - Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:\_\_\_\_\_
  - Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents and case report forms for dosing, whether the **randomization schedule was followed for dosing of subjects**, etc.)
  - Other Comments:
- 
- 

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**ANALYTICAL**

**Study Number:** GS-US-216-0115

**Analytical Site:**



**Investigator:**

**Methodology:** LC-MS/MS

**Study Number:** GS-US-216-0116

**Analytical Site:**



**Investigator:**

**Methodology:** LC-MS/MS

**Please confirm the following during the inspection:**

- All pertinent items related to the analytical method used for the measurement of darunavir concentrations for the study **GS-US-216-0115** and cobicistat concentrations for the study **GS-US-216-016** in human plasma should be examined.
- The accuracy of the analytical data provided in the NDA submission by the applicant should be compared with the original documents at the site.
- **The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC, demonstration of accuracy and precision in matrix using standards and QCs prepared from separate stocks, stability of subject samples covered by validated stability period.**
- **Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.**
- **At least one demonstration of precision and accuracy from QCs and calibrators prepared from separate stock solutions.**
- **Scrutinize the number of repeat assays of the subject plasma samples, and the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like freeze thaw cycles sufficiently covered the stability of reanalyzed subject samples.**

In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Furthermore, please focus on the following during the inspection:

**Study GS-US-216-0115:**

The darunavir and ritonavir method validated at (b) (4) is a partial validation of a method originally validated (b) (4)

(b) (4)

1) Although this NDA is for cobicistat, please inspect the method validation and bioanalysis of subject samples pertaining to darunavir. The ritonavir analyzed at (b) (4) and the cobicistat analyzed at (b) (4) do not require inspection.

2) No stability experiments were conducted by (b) (4). Therefore, OCP has requested that we determine if the extrapolation of stability data generated by other labs is

acceptable, and if the same darunavir method was used by these labs.

3) Section 1 of darunavir and ritonavir bioanalytical report for GS-US-216-115 includes the following statement:

"Pre-study discussions refer to SH09-J01-TR403".

Please investigate whether there is any information relevant to GS-US-216-115 for darunavir samples in that document.

4) The darunavir and ritonavir bioanalytical report for GS-US-216-115 indicated that IS response falls within 25%-175% of the mean IS response. Please evaluate the actual IS variability for all the runs.

5) Please investigate the reasons for the failure (b) (4) (b) (4) for darunavir samples.

(b) (4)

**Study GS-US-216-0116:**

1) Study GS-US-216-0116 relates to bioanalysis of cobicistat.

2) The elvitegravir, ritonavir, midazolam, and 1'-hydroxymidazolam were analyzed along with cobicistat from Treatment C in GS-US-216-0116 that were analyzed by (b) (4) do not require inspection.

3) During cobicistat method validation (b) (4) project 60-0949), in Table 23, for post-preparative reinjection reproducibility multiple QCs at 200 ng/mL have %RE >15%. No explanation was provided for this observation in the method validation report. Please evaluate whether any of the cobicistat samples from Treatment A or B was stored prior to initial injection or were re-injected and are impacted by this observation (e.g. plasma concentration values should be excluded from the reported PK data).

**Additional instructions to ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGC POC prior to the inspection. Therefore, we request that the DBGC POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the DBGC POC for inspection-related questions or clarifications.

**Please fax/email a copy of Form FDA-483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of the inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to the observations listed on Form FDA-483. Please forward the written response as soon as you receive it to Dr. Sam H. Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).**

Head Quarters Contact: Young Moon Choi, Ph.D.  
Young.choi@fda.hhs.gov  
Tel: (301) 796-1516  
FAX: (301)-847-8748

DDFI Contact: Arindam Dasgupta, Ph.D.  
arindam.dasgupta@fda.hhs.gov  
Tel: (301)-796-3326  
FAX: (301)-847-8748

cc:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Patel/Mada/Choi/Dasgupta/Dejernett/CF

ORA HQ DFFI IOB BIMO/Turner, Cheryl A/Arline, Yvett

D/Montemurro, Ann M/Alexis, Praxede/Braswell, Dyrene/Johnson,  
Percilla/Colon, Hector

ORA FLA-DO DIB/ Kathleen Sinninger/ BIMO/Brunilda Torres

ORA PHI-DO DIB/ Karyn Campbell/ BIMO/Daniel Tammariello/Cynthia  
Rakestraw

ORA SEA-DO DIB/ Celeste Corcoran/ BIMO/Annette Melendez/Virginia  
Meeks

Draft: JP 9/28/2012; YMC 10/24/2012

Edit: SRM: 10/25/2012; SHH 10/26/2012

OSI file #6384; O:\BE\assigns\bio203094.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: (b) (4)

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/s/  
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YOUNG M CHOI  
10/26/2012

SAM H HAIDAR  
10/31/2012

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

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 203094/0

**Application Type:** New NDA

**Name of Drug:** cobicistat tablet (Proprietary Name: TYBOST conditionally granted)

**Applicant:** Gilead Sciences, Inc.

**Submission Date:** June 27, 2012

**Receipt Date:** June 28, 2012

## **1.0 Regulatory History and Applicant's Main Proposals**

The original application for NDA 203094, cobicistat 150 mg tablet was submitted on June 27, 2012, as a pharmacokinetic enhancer of HIV-1 protease inhibitors atazanavir and darunavir for the treatment of HIV-1 infection in adults. Cobicistat is a cytochrome P4503A inhibitor studied under IND 101283.

## **2.0 Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft 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).

## **3.0 Conclusions/Recommendations**

No SRPI format deficiencies were identified in the review of this PI. However, the following revisions outside the scope of the SRPI will be conveyed to the sponsor in the 74-day letter.

### Under Highlights

1. The following information should be deleted from the Use in Specific Populations section:
  - a. Pediatrics: Not recommended for patients less than 18 years of age. (8.4)

Abiola Olagundoye-Alawode, PharmD  
Regulatory Project Manager

September 5, 2012  
Date

Karen Winestock  
Chief, Project Management Staff

September 5, 2012  
Date

## Selected Requirements of Prescribing Information (SRPI)

### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

---

## Highlights (HL)

### GENERAL FORMAT

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

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

**YES**

6. Section headings are presented in the following order in HL:

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

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

*Comment:*

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

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

*Comment:*

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

*Comment:*

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

*Comment:*

#### Initial U.S. Approval

**YES**

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

*Comment:*

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

- N/A** 12. All text must be **bolded**.  
Comment:
- N/A** 13. Must have a centered 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**”).  
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.  
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
Comment:
- N/A** 20. 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

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”  
Comment:

## Selected Requirements of Prescribing Information (SRPI)

### Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. 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

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
*Comment:*
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
*Comment:*
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
*Comment:*
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
*Comment:*
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
*Comment:*
- YES** 35. 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:*

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
*Comment:*
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
*Comment:*
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. 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 patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. 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

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. 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**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is 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 clinical practice.”*

**Comment:**

- N/A** 47. When postmarketing adverse reaction data is 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

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

---

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ABIOLA M OLAGUNDOYE-ALAWODE  
09/05/2012

KAREN D WINESTOCK  
09/06/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203094 BLA#	NDA Supplement #: BLA Supplement #	Efficacy Supplement Type SE
Proprietary Name: TYBOST (conditionally granted) Established/Proper Name: cobicistat Dosage Form: Tablet Strengths: 150mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): Naomi Kautz, M.Sc., Senior Manager, Regulatory Affairs		
Date of Application: June 27, 2012 Date of Receipt: June 28, 2012 Date clock started after UN:		
PDUFA Goal Date: April 26, 2013		Action Goal Date (if different):
Filing Date: August 27, 2012		Date of Filing Meeting: July 30, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only)– 5 (New Formulation)		
Proposed indication(s)/Proposed change(s): Pharmacokinetic enhancer of HIV-1 protease inhibitors atazanavir and darunavir.		
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><b>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>		
<i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>		
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><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>		

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): IND 101283, IND 62477, NDA 203100, NDA 21976, DMFs <sup>(b) (4)</sup> , <sup>(b) (4)</sup> , 25188				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b> 5 years if approved before NDA 203100; or 3 years if approved after NDA 203100.</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			5 years if approved before NDA 203100; or 3 years if approved after NDA 203100.
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

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

(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)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<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>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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&amp;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>	X			Signed by Andrew Cheng, SVP, HIV Therapeutics & Development Operations
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic submission only
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u></p> <p>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></p> <p><i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>		X		
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	X			Partial waiver included for children from birth < 3 months of age Request deferral for subjects 3 months to < 18 years of age.
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			TYBOST has been conditionally approved
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<b><u>Prescription Labeling</u></b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU)			

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

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

	<input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) Access Program labels			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?			X	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			PPI consult sent to PLT- Sharon Mills is the reviewer. PI, and carton/ container label sent to OSE/DMEPA, Morgan Walker is the reviewer. Consult sent to DDMAC for PI, PPI and carton/container, Jessica Fox/Kemi Asante are the reviewers
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample			

4

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

	<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>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
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>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? <b>Date(s):</b> March 12, 2010  Preliminary comments sent March 10, 2010 Meeting minutes sent April 9, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			Meeting to review the nonclinical, Phase 1 and Phase 2 clinical data and to receive comments on Phase 3 studies of GS-9350.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> March 30, 2012 meeting was cancelled <i>If yes, distribute minutes before filing meeting</i>		X		The March 30, 2012 pre-NDA meeting was cancelled by the sponsor after receiving our March 27, 2012, preliminary comments
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> IND 101283: receipt date April 16, 2009 submitted mouse and rat  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Final report from Executive CAC on May 27, 2009

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 30, 2012

**BLA/NDA/Supp #:** 203094

**PROPRIETARY NAME:** TYBOST (conditionally granted)

**ESTABLISHED/PROPER NAME:** cobicistat

**DOSAGE FORM/STRENGTH:** 150 mg tablet

**APPLICANT:** Gilead Sciences, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Pharmacokinetic enhancer of HIV-1 protease inhibitors atazanavir and darunavir.

**BACKGROUND:** The original application for NDA 203094, cobicistat 150 mg was submitted on June 28, 2012 to be used as a pharmacokinetic enhancer of HIV-1 protease inhibitors atazanavir and darunavir. Cobicistat is a cytochrome P4503A inhibitor studied under IND 101283.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Abiola Olagundoye-Alawode	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Clinical	Reviewer:	Peter Miele	Y
	TL:	Linda Lewis	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	n/a	
	TL:	n/a	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	n/a	
	TL:	n/a	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Takashi Komatsu	Y

	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	Stanley Au	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Yanming Yin	N
	TL:	Fraser Smith	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Laine Myers	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	n/a	
	TL:	n/a	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	n/a	
	TL:	n/a	
Product Quality (CMC)	Reviewer:	Fuqiang Liu	N
	TL:	Stephen Miller	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	n/a	
	TL:	n/a	
CMC Labeling Review	Reviewer:	n/a	
	TL:	n/a	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Morgan Walker	Y
	TL:	Jamie Wilkins Parker	Y
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	Y
	TL:	Barbara Fuller	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Deepika Lakhani, Biopharmaceutics Jeffrey Florian, Pharmacometrics		Y Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> No issues identified</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>or efficacy issues</i></li> <li>○ <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></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Information request sent 8/13/12</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"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Inspection of facility??</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Waiting on ONDQA</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Jeffrey Murray, M.D.	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): November 29, 2012	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<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, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody 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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

Abiola Olagundoye-Alawode

8/22/12

Regulatory Project Manager

Date

Karen Winestock

8/22/12

Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ABIOLA M OLAGUNDOYE-ALAWODE  
08/24/2012

KAREN D WINESTOCK  
08/24/2012