

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203094 Original 1

SUPPL #

HFD #

Trade Name TYBOST

Generic Name cobicistat

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known 9/24/14

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

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

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

3 yrs

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

YES NO

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

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

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA# 203100

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

GS-US-216-0114 and GS-US-216-0105

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

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

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation 1 - GS-US-216-0114

Investigation 2 - GS-US-216-0105

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 101283 YES !
! ! NO
! Explain:

Investigation #2
IND # 101283 YES !
! ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

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

/s/

KAREN D WINESTOCK
09/24/2014

DEBRA B BIRNKRANT
09/24/2014

EXCLUSIVITY SUMMARY

NDA # 203094 Original 2

SUPPL #

HFD #

Trade Name TYBOST

Generic Name cobicistat

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known 9/24/14

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

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Study -GS-US-216-0115 is a multidose trial that compared the exposure of cobicistat plus darunavir to the exposures observed with the approved ritonavir plus darunavir dosing regimen. The study enrolled healthy volunteers. .

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

3

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

YES NO

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YES NO

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

NDA# 203100

STRIBILD

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

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

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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

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

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Karen Winestock
Title: Chief, Project Management Staff
Date: 9/23/14

Name of Office/Division Director signing form: Debra Birnkrant
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KAREN D WINESTOCK
09/24/2014

DEBRA B BIRNKRANT
09/24/2014

Debarment Certification

Gilead Sciences, Inc. 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 (NDA 203-094, COBI tablets).

[See appended electronic signature]

Andrew Cheng, MD, PhD
SVP, HIV Therapeutics & Development Operations
Gilead Sciences, Inc.

1.3.3 Debarment Certification

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd hh:mm)
Andrew Cheng	Clinical eSigned	2012-01-04 10:20

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203094 Original 1 BLA #	NDA Supplement # 0 BLA Supplement #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Tybost Established/Proper Name: cobicistat Dosage Form: 150 mg tablet		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):
RPM: Karen Winestock		Division: Division of Antiviral Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 28, 2014</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None CR 4/26/13	

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

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

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

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

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

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	September 25, 2014
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP Sept. 24, 2014 CR April 26, 2013
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Sept. 17, 2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 27, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	9/19/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 27, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Sept. 15, 2014
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Letters- 6/14/14 & 9/21/12 Reviews June 11, 2014 March 12, 2013 September 21, 2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 9/6/12 <input checked="" type="checkbox"/> DMEPA 9/17/14, 6/6/14, 11/16/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 8/8/14 & 3/20/2013 <input checked="" type="checkbox"/> ODPD (DDMAC)8/26/14, 8/18/14 3/20/13 3/19/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review- August 24, 2012 <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included 9/24/14
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>April 3, 2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg Pre-NDA meeting preliminary comments (March 27, 2012)
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg April 9, 2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/26/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04/4/13 & 8/25/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 4 PMRs
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	8/5/14 9/10/13 & 3/22/13 August 15, 2012 (Filing review)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Included in clinical review (page 21)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None 9/11/14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested February 28, 2013, December 6, 2012;. December, 5, 2012;
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/15/14, 3/11/14; 3/10/13 July 21, 2012 (Filing review)
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 25, 2013
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 19, 2013; August 8, 2012 (Filing review)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/19/13, 3/22/13; August 20, 2012 (Filing review)
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None April 17, 2013
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 21, 2013; August 1, 2012 (Filing review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc March 27, 2013
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None March 27, 2013
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/1/14,
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/6/14, 4/25/13, 3/19/13, 9/25/12, (August 28, 2012 Filing review), Biopharmaceutics review- March 19, 2013
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See Product Quality Review- March 19, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 4/25/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

KAREN D WINESTOCK
09/25/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203094 Original 2 BLA #	NDA Supplement # 0 BLA Supplement #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Tybost Established/Proper Name: cobicistat Dosage Form: 150 mg tablet		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):
RPM: Karen Winestock		Division: Division of Antiviral Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 28, 2014</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None CR 4/26/13	

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

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

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

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

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

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	September 25, 2014
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP Sept. 24, 2014 CR April 26, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Sept. 17, 2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 27, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	9/19/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 27, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Sept. 15, 2014
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Letters- 6/14/14 & 9/21/12 Reviews June 11, 2014 March 12, 2013 September 21, 2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 9/6/12 <input checked="" type="checkbox"/> DMEPA 9/17/14, 6/6/14, 11/16/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 8/8/14 & 3/20/2013 <input checked="" type="checkbox"/> ODPD (DDMAC)8/26/14, 8/18/14 3/20/13 3/19/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review- August 24, 2012 <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included 9/24/14
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>April 3, 2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg Pre-NDA meeting preliminary comments (March 27, 2012)
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg April 9, 2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/26/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04/4/13 & 8/25/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 4 PMRs
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	8/5/14 9/10/13 & 3/22/13 August 15, 2012 (Filing review)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Included in clinical review (page 21)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None 9/11/14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested February 28, 2013, December 6, 2012;. December, 5, 2012;
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/15/14, 3/11/14; 3/10/13 July 21, 2012 (Filing review)
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 25, 2013
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 19, 2013; August 8, 2012 (Filing review)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/21/14, 4/19/13, 3/22/13; August 20, 2012 (Filing review)
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None April 17, 2013
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None March 21, 2013; August 1, 2012 (Filing review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc March 27, 2013
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None March 27, 2013
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/1/14,
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/6/14, 4/25/13, 3/19/13, 9/25/12, (August 28, 2012 Filing review), Biopharmaceutics review- March 19, 2013
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See Product Quality Review- March 19, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 4/25/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

KAREN D WINESTOCK
09/25/2014

From: Winestock, Karen
To: [Christophe Beraud \(Christophe.Beraud@gilead.com\)](mailto:Christophe.Beraud@gilead.com)
Subject: NDA 203094 Original 1 & 2 PI and PPI
Date: Wednesday, September 17, 2014 12:32:00 PM
Attachments: [203094 Original 1 and Original 2 PI PPI.v.4.docx](#)

Dear Christophe,

The Agency's latest PI changes are attached. At this time, we do not have any additional PPI changes. Please review our proposed changes and provide a response by close of business Friday, September 19, 2014, if possible.

I note the following, Gilead has changed e.g. to eg throughout the labeling, however, that abbreviation is not listed in the dictionary.

*Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500*

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

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/s/

KAREN D WINESTOCK
09/17/2014

From: Winestock, Karen
To: [Christophe Beraud \(Christophe.Beraud@gilead.com\)](mailto:Christophe.Beraud@gilead.com)
Subject: NDA 203094 Original 1 & 2 PI, PPI, and DHCP letter
Date: Friday, September 05, 2014 10:28:00 AM
Attachments: [203094 Original 1 and 2 PI PPI.v3.doc](#)
[DGHCP letter.v2.doc](#)

Good morning,

The FDA's latest labeling and DHCP revisions are attached. If possible, please provide Gilead's response by Thursday, September 11, 2014.

In addition, I noticed that your manufacturer information is not at the end of the PI, please confirm that the PI and PPI are not separate documents. If they are, you need to add the manufacturers information to the end of the PI.

Please acknowledge receipt of this communication.

Thank you,

*Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500*

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/s/

KAREN D WINESTOCK

09/17/2014

Labeling and DHCP letter emailed to Gilead on 9.5.14



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2013

To: Naomi Kautz, M.Sc. Senior Manager, Regulatory Affairs	From: Stacey Min, Pharm.D. Division of Antiviral Products
Company: Gilead Sciences, Inc.	Title: Regulatory Project Manager
Fax number: 650-522-5489	Fax number: 301-796-9883
Phone number: 650-522-2789	Phone number: 301-796-4253

Subject: NDA 203094 and NDA 203093 Comments on safety update for resubmission

Total number of pages including cover: 3

Comments:

Document will not be faxed or mailed. This facsimile will be provided by electronic mail. Please reply by email to acknowledge receipt.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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MEMORANDUM OF FACSIMILE:

Date: September 17, 2013

NDA: 203094
203093

Drug: TYBOST (cobicistat)
VITEKTA (elvitegravir)

To: Naomi Kautz, M.Sc., Senior Manager, Regulatory Affairs
Perena Menon, Ph.D., Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Stacey Min, Pharm.D., Senior Regulatory Project Manager and
Pat Hong, M.S., Senior Regulatory Project Manager

Subject: NDA 203094 and NDA 203093 Comments on Proposed Safety
Update for Resubmission

Please refer to your NDA 203094 for TYBOST (cobicistat) and NDA 203093 for VITEKTA (elvitegravir). We also refer to your August 13, 2013 submission to both the NDAs requesting feedback on your proposed safety update for your resubmission for cobicistat and elvitegravir. We have reviewed your submission agree that your proposal is acceptable if you follow the same format as the original Safety Update, including a summary of new data since the original NDA submission. Please confirm that the trials being included are similar to those in the Safety Update for the original NDA submission.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

STACEY MIN
09/17/2013

From: Winestock, Karen
To: [Christophe Beraud \(Christophe.Beraud@gilead.com\)](mailto:Christophe.Beraud@gilead.com)
Bcc: [Struble, Kimberly](#); [Seo, Shirley](#); [Au, Stanley](#); [Boyd, Sarita](#)
Subject: FW: NDA 203094 Original 1 and Original 2: Pi, PPI, DHP LTR and PMR comments
Date: Friday, August 01, 2014 4:18:00 PM
Attachments: [203094 Original 1 and 2 PI PPI.doc](#)
[DGHCP letter.doc](#)

Good afternoon Dr. Beraud,

We have reviewed your proposed labeling (package insert and patient package insert) and the Dear Health Care Professional letter and the Agency's proposed revisions are provided in the attached documents. Please submit your response no later than August 11, 2014.

In addition, we have reviewed your July 25, 2014, response to our PMC/PMR Discussion comments and we would like to receive your justification for submitting the drug-drug interaction protocols in 2015. Please submit your response no later than August 7, 2014.

Please confirm receipt of this message.

Sincerely,

*Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500*

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

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/s/

KAREN D WINESTOCK
08/01/2014



NDA 203094 Original 1

PMR/PMC DISCUSSION COMMENTS

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application dated June 27, 2012 and to your resubmission dated March 28, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tybost (cobicistat) tablet, 150 mg.

We also refer to our April 11, 2013 postmarketing requirement (PMR), letters and to your April 16, 2013 response. It has been approximately one year since we received your PMR response and your timelines may have changed. We are requesting you provide an updated response for the following PMRs:

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.

PMR Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion	MM/YYYY
	Study Report Submission	MM/YYYY

2. PMR - Conduct a clinical trial in healthy subjects 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 contraceptives.

PMR Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion	MM/YYYY
	Study Report Submission	MM/YYYY

3. PMR – Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin.

PMR Schedule Milestones: Final Protocol Submission: MM/YYYY
Study/Trial Completion MM/YYYY
Study Report Submission MM/YYYY

4. PMR – Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin.

PMR Schedule Milestones: Final Protocol Submission: MM/YYYY
Study/Trial Completion MM/YYYY
Study Report Submission MM/YYYY

Please submit your response by July 25, 2014.

If you have any questions, call me, at (301) 796-0834 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Drug Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KAREN D WINESTOCK
07/18/2014



NDA 203094 Original 2

PMR/PMC DISCUSSION COMMENTS

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 27, 2012, and to your resubmission dated April 3, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tybost, (cobicistat) tablet, 150 mg.

We have the following proposed Postmarketing Requirements:

CLINICAL PHARMACOLOGY

1. Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of once daily darunavir and cobicistat (DRV/COBI) combined with a background regimen in HIV-1 treatment experienced 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 pharmacokinetic (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 plus background regimen, assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

PMR Schedule Milestones: Protocol Submission: Month/Year
Study/Trial Completion: Month/Year
Final Report Submission: Month/Year

2. Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of the estrogen and progesterin components of a combined oral contraceptives.

PMR Schedule Milestones: Protocol Submission: Month/Year
Study/Trial Completion: Month/Year
Final Report Submission: Month/Year

3. Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin.

PMR Schedule Milestones: Protocol Submission: Month/Year
Study/Trial Completion: Month/Year
Final Report Submission: Month/Year

4. Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin.

PMR Schedule Milestones: Protocol Submission: Month/Year
Study/Trial Completion: Month/Year
Final Report Submission: Month/Year

Please submit your response by July 25, 2014.

If you have any questions, call me, at (301) 796-0834 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KAREN D WINESTOCK
07/18/2014

Winestock, Karen

From: Winestock, Karen
Sent: Monday, June 30, 2014 10:45 AM
To: Christophe Beraud (Christophe.Beraud@gilead.com)
Subject: NDA 203094 Original 1 and 2 - Dear Healthcare Provider Letter

Good morning,

We acknowledge receipt of your pdf version of the Dear Healthcare Provider letter, but we are unable to locate a word version. If a word version was not submitted with the resubmissions, please update your application with this version no later than July 11, 2014. If a word version was submitted, please identify the date of the submission?

Thank you,

*Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500*



NDA 203094

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Christophe Beraud, Ph.D.
Director, Regulatory Affairs

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 27, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cobicistat Tablets, 150 mg.

We also refer to:

- Your correspondence dated and received June 28, 2012, requesting review of the proposed proprietary name, "Tybost"
- Our letter dated September 21, 2012, stating that your proposed proprietary name was conditionally acceptable
- Our Complete Response Action Letter dated April 26, 2013
- Your NDA Resubmission dated and received March 28, 2014

Finally, we refer to your correspondence dated and received April 9, 2014, requesting review of your proposed proprietary name, Tybost. We have completed our review of the proposed proprietary name Tybost, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your April 9, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Chief of Project Management in the Office of New Drugs (OND), Karen Winestock, at (301) 796-0834.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
06/13/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
06/14/2014

From: Winestock, Karen
To: prerna.menon@gilead.com
Cc: [Mani, Nina](#)
Subject: NDA 203094 Original 1 and Original 2 - Safety Update
Date: Tuesday, April 29, 2014 11:44:00 AM

Dear Dr. Menon,

The clinical reviewer is reviewing the safety update report included in the March 26, 2014 submission and the following questions, comments and requests for additional information are being conveyed to you on their behalf:

Do the numbers in the "Original NDA" column in the Resubmission Safety Update document include the 120-day safety update information submitted in October 2012?

Is there a mechanism to determine which narratives pertain to events that occurred since the original NDA, including the 120-day safety update? The narratives provided in module 5.3.5.3 appear to contain events to date, rather than those which occurred during the resubmission safety update period between the original NDA/120-day safety update and the resubmission. If no mechanism exists as submitted, please provide the patient ID numbers for the new treatment-emergent SAEs and AEs leading to discontinuation not included in the original NDA or 120-day safety update in the ATV/co group for Studies GS-US-216-0114 and GS-US-216-0105.

Please acknowledge receipt of this message.

Sincerely,

*Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500*

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/s/

KAREN D WINESTOCK
04/29/2014



NDA 203094

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Christophe Beraud, Ph.D.
Director, Regulatory Affairs

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 27, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cobicistat, Tablets, 150 mg.

We also refer to:

- Your correspondence dated and received June 28, 2012, requesting review of the proposed proprietary name, "Tybost"
- Our Proprietary Name Conditionally Acceptable letter to Gilead Sciences, Inc. dated September 21, 2012
- Our Complete Response letter dated April 26, 2013
- Your NDA Resubmission dated and received March 28, 2014

Finally, we refer to your correspondence dated and received April 9, 2014, requesting a review of your proposed proprietary name, Tybost. Upon preliminary review of your submission, we have determined that it is a complete submission as described in our Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

Therefore, the user fee goal date is July 8, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Karen Winestock, Chief, Project Management Staff in the Office of New Drugs, at (301) 796-0834.

Sincerely,

{See appended electronic signature page}

Danyal Chaudhry, M.P.H.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
04/14/2014



NDA 203094 Original 1

**ACKNOWLEDGE -
CLASS 2 COMPLETE RESPONSE**

Gilead Sciences, Inc.
Attention: Christophe Beraud, PhD
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

We acknowledge receipt on March 28, 2014, of your March 28, 2014, resubmission to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cobicistat tablet 150 mg.

We consider this resubmission a complete, class 2 response to our action letter. Therefore, the user fee goal date is September 28, 2014.

If you have any questions, call me, at (301) 796-0834 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KAREN D WINESTOCK
04/10/2014



NDA 203094 Original 2

**ACKNOWLEDGE -
CLASS 2 COMPLETE RESPONSE**

Gilead Sciences, Inc.
Attention: Christophe Beraud, PhD
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

We acknowledge receipt on April 3, 2014, of your April 3, 2014, resubmission to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cobicistat tablet 150 mg.

We consider this resubmission a complete, class 2 response to our action letter. Therefore, the user fee goal date is October 3, 2014.

If you have any questions, call me, at (301) 796-0834 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KAREN D WINESTOCK
04/10/2014



NDA 203094 Original 2

ACKNOWLEDGE INCOMPLETE RESPONSE

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

We acknowledge receipt on March 26, 2014 of your March 26, 2014 submission to your new drug application (NDA) for (cobicistat) tablets, 150 mg.

We do not consider this a complete response to our April 26, 2013 action letter. Therefore, we will not start the review clock until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

- Datasets for Studies GS-US-216-0115 and GS-US-216-0116 that address the bioanalytical 483 observations need to be submitted to the Original 2 submission.

If you have questions, call Karen Winestock, Chief, Project Management Staff, at (301) 796-0834.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
04/09/2014

From: Winestock, Karen
To: [Christophe Beraud \(Christophe.Beraud@gilead.com\)](mailto:Christophe.Beraud@gilead.com)
Cc: [Mani, Nina](#)
Subject: RE: NDA203094 Original 2 (cobicistat)-PK datasets
Date: Monday, April 07, 2014 2:28:00 PM

Good afternoon,

We refer to the April 3, 2014, submission to NDA 203094 Original 2, which provided the clinical pharmacology data sets for Studies GS-US-216-0115 and GS-US-216-0116 and the clinical pharmacology team has the following request for additional information:

1. In reviewing the 216-0116adpkconc_req5992.xpt and the 216-0116adpkparm_req5992.xpt data files, it does not appear that either the cobicistat concentrations or cobicistat PK parameters were excluded for subjects 2037 and 2038. Please clarify the discrepancy between the written resubmission responses which stated these two subjects were excluded and the cobicistat PK information provided in the datasets for the GS-US-216-116 trial.

Please provide the requested information by 10:00 a.m., Tuesday, April 8, 2014.

Please acknowledge receipt of this message.

Sincerely,

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500

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/s/

KAREN D WINESTOCK
04/07/2014

From: Winestock, Karen
To: [Christophe Beraud \(Christophe.Beraud@gilead.com\)](mailto:Christophe.Beraud@gilead.com); "prerna.menon@gilead.com"
Cc: [Mani, Nina](#)
Subject: FW: NDA203094 Original 2 (cobicistat)-PK datasets
Date: Wednesday, April 02, 2014 12:50:00 PM

Good afternoon,

Karen Winestock (primary) and Nina Mani(secondary) will be the regulatory project managers for NDA 203094 Original 1 and Original 2. All questions related to these submissions should be forwarded to my attention and if I am out of the office, please contact Dr. Mani.

We refer to the March 26, 2014 resubmission to NDA 203094/Original 2. According to your cover letter, the revised and original clinical pharmacology datasets for Studies GS-US-216-0115 and GS-US-216-0116 were provided in Module 1.11.3. We are unable to locate the datasets in this module. Please provide the location of these datasets by 3:00 pm, Wednesday, April 2, 2014.

Please acknowledge receipt of this message.

Sincerely,

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Center for Drug Evaluation and Research
301-796-0834 or 301-796-1500

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/s/

KAREN D WINESTOCK
04/02/2014



NDA 203094

WRITTEN REQUEST

Gilead Sciences, Incorporated
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 26, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for cobicistat tablets, 150 mg.

We also refer to your May 7, 2012 Proposed Pediatric Study Request for cobicistat.

These requested studies investigate the potential use of cobicistat as an inhibitor of CYP3A-mediated metabolism of the HIV-1 protease inhibitors atazanavir and darunavir in pediatric patients.

BACKGROUND

Currently in the United States, the Center for Disease Control (CDC) estimates that each year, 100 to 200 infants with HIV-1 infection are born in the United State. Perinatal transmission of HIV-1 accounts for virtually all new infections in preadolescent children. Rates of perinatal transmission have decreased dramatically in the U.S. since the 1990s due to effective perinatal prophylaxis regimens including combination antiretroviral treatment of pregnant women. However, perinatal transmission of HIV-1 remains a serious global public health threat with an estimated 3.3 million pediatric patients living with HIV/AIDS, of whom greater than 90% reside in sub-Saharan Africa. The World Health Organization estimates that fewer than 30% of pediatric patients living with HIV/AIDS in low- and middle-income countries are currently receiving antiretroviral therapy but that number is growing steadily.

Transmission of HIV-1 among adolescents is attributable to adult risk-associated behaviors, primarily due to sexual exposure. According to CDC estimates published in 2011, there was a 21% increase in HIV incidence among people 13 to 29 years of age between 2006 and 2009. This age group accounted for 39% of new HIV diagnoses during this period, with the highest rate observed in young black/African American males.

Combination antiretroviral therapy containing an “anchor” drug and “backbone” of two nucleoside reverse transcriptase inhibitors (NRTIs), is standard treatment for HIV-1 infection in treatment-naive adult and pediatric patients. Effective antiretroviral therapy results in a reduction in viral load

as measured by quantification of HIV-1 RNA with a concomitant increase in the CD4⁺ cell count. Improvement in these markers has been shown to be associated with declining morbidity and mortality.

Many of the currently approved protease inhibitors (PIs) achieve higher exposure and less variability when given in combination with ritonavir (RTV), another PI that is a potent inhibitor of CYP3A-mediated drug metabolism. Concomitant administration of low-dose RTV as a pharmacoenhancer has allowed use of lower doses and longer dosing intervals of the codministered PIs and has provided improved treatment outcomes. However, use of RTV in this role has both potential and proven disadvantages. RTV is associated with substantial gastrointestinal (GI) intolerance and poor palatability, even at the lower doses used as pharmacokinetic enhancer. In addition, RTV is also an HIV-1 PI and may have some impact on resistance development pathways and cross-resistance.

Investigators have expressed need for other pharmacoenhancer products with a better safety profile and without intrinsic anti-HIV activity. Cobicistat (COBI) was developed to address these needs. Like RTV, cobicistat is a potent CYP3A inhibitor and functions to increase the systemic exposure of the coadministered PI. It has been developed for use in combination with atazanavir (ATV) or darunavir (DRV), both approved PIs currently indicated for coadministration with RTV. Cobicistat represents the first product reviewed in the Division of Antiviral Products (DAVP) that has no intrinsic antiviral properties but will be indicated only for the purpose of increasing exposure of an active drug.

The mechanism of action of cobicistat is age-dependent; expression of CYP3A4/5 is low at birth and subsequently increases to reach adult levels of activity in later years. The specific age at which CYP3A4/5 expression reaches adult levels of activity is uncertain. Therefore, information on the appropriate cobicistat dosage regimen in different pediatric age groups is critical in determining whether sufficient CYP3A4/5 inhibition is achieved. Functionally, the appropriate dose of cobicistat will need to be assessed based on the exposure of the coadministered protease inhibitor (ATV or DRV).

We expect a pediatric supplement to be based on extrapolation of efficacy from the adult clinical trials of cobicistat-boosted PIs, with bridging pharmacokinetic and safety data provided in the requested pediatric trial. In this case, the antiviral effect is attributed to ATV or DRV when coadministered with cobicistat. The extrapolation of efficacy for antiretroviral drugs is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects¹. The DAVP agrees that HIV-1 disease in pediatric subjects is similar but not identical to adult HIV-1 disease² noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. However, the

¹ 21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355

² Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468

pathophysiology of immune system destruction by HIV-1 is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV-1 disease consist of both severe manifestations of common pediatric infections and also opportunistic infections similar to those seen in HIV-1-infected adults.

In pediatric and adult subjects, treatment of HIV-1 disease is monitored using the same two surrogate markers, CD4⁺ cell count and HIV-1 RNA (viral load) measured by PCR. Antiretroviral drugs, including PIs coadministered with RTV or cobicistat, have been shown to lower HIV-1 RNA, improve CD4⁺ cell counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011; pp 1-268³).

We are waiving the pediatric study requirement for neonates and pediatric patients younger than 3 months of age because studies in this age group are impossible or highly impracticable and neither ATV nor DRV are being developed in this age group. ATV is associated with increases in serum bilirubin and will not be developed in infants less than 3 months because of the potential for kernicterus. DRV was associated with unacceptable toxicity observed in a juvenile rat toxicity study and will not be developed in pediatric patients younger than 3 years. The studies required by this WR will conform to the age limitations of ATV and DRV, as stated above.

To obtain needed pediatric information on cobicistat, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies):*

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1: An open-label pediatric pharmacokinetic (PK), safety, and antiviral activity trial of once daily ATV/COBI or once daily DRV/COBI combined with a background regimen in HIV-1 pediatric subjects from 3 months to less than 18 years of age (for ATV/cobicistat) and 3 years to less than 18 years of age (for DRV/cobicistat) who have suppressed viremia (HIV-1 RNA < 50 copies/mL at screening) on a stable ATV/RTV or DRV/RTV regimen for at least 3 months prior to screening. Subjects with CD4⁺ cell counts less than 200 cells/mm³ at screening and those with an AIDS defining condition with onset within 30 days before screening will be excluded from the study.

Part A of the study will assess the steady state pharmacokinetics of ATV or DRV when each is coadministered with RTV followed by an assessment of ATV or DRV

³ Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PediatricGuidelines.pdf>.

pharmacokinetics when each is coadministered with COBI. Subjects with suppressed viremia on a stable ATV/RTV or DRV/RTV regimen will be switched to the corresponding ATV/COBI or DRV/COBI regimen following the first pharmacokinetic assessment (with RTV). Four age cohorts will be assessed sequentially beginning with the oldest cohort for ATV/COBI and three age cohorts will be assessed sequentially beginning with the oldest cohort for DRV/COBI. Following completion of the ATV/COBI or DRV/COBI pharmacokinetic assessment, subjects will have the option to remain on their ATV/COBI or DRV/COBI regimen for up to 48 weeks with long-term follow-up available.

After confirmation of acceptable ATV or DRV PK based on Day 10 data in Part A, Part B of the study will enroll additional subjects in each age group. Additionally, enrollment of Part A subjects for the next age cohort can be initiated. Part B will assess long-term safety and antiviral activity of ATV/COBI or DRV/COBI plus the background regimen, for 48 weeks with long-term follow-up available. Subjects entering Part B directly must also have suppressed viremia (HIV-1 RNA < 50 copies/mL at screening) on a stable ATV/RTV or DRV/RTV regimen for at least 3 months prior to screening. Activity will be assessed on the basis of continued HIV-1 RNA virologic response and safety monitoring over at least 24 weeks of dosing. Plans for long-term follow-up to assess laboratory and clinical safety parameters, growth, and development over a period of 5 years must be incorporated into the study but results are not required to be submitted to fulfill this Written Request (i.e., long-term follow-up data may be provided in a later submission).

- Efficacy of COBI when coadministered with ATV in pediatric subjects 3 months to less than 18 years of age or DRV in pediatric subjects 3 years to less than 18 years of age will be supported by achieving drug exposure of ATV or DRV in pediatric subjects similar to those found to be safe and effective in adults receiving ATV/RTV or DRV/RTV and should not be lower than any approved pediatric ATV/RTV or DRV/RTV regimen in any population.
- *Objective of each study:*
 - Study 1:* The objective of this study will be to determine the pharmacokinetic and safety profile of COBI coadministered with ATV in HIV-1-infected pediatric subjects from 3 months to less than 18 years of age and DRV in HIV-1-infected pediatric subjects from 3 years to less than 18 years of age, identify an appropriate dose (or doses) of COBI to achieve target ATV or DRV exposure in HIV-1-infected pediatric subjects across the age range, and confirm the antiviral activity of this dose (or doses) in a treatment regimen.
- *Patients to be studied:*
 - *Age group in which study(ies) will be performed:*

Study 1: 3 months to less than 18 years, divided into 4 cohorts for ATV/COBI and 3 years to less than 18 years of age divided into 3 cohorts for DRV/COBI

- *Number of patients to be studied:*

Study 1: a minimum of 54 in Part A and a minimum of 100 in Part B; subjects successfully completing Part A may enroll in Part B and be included in the total number for Part B.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

- *Pharmacokinetic Endpoints:*

Study 1: The pharmacokinetic endpoints for Part A of the study must include parameters such as C_{max} , C_{tau} , T_{max} , $t_{1/2}$, $AUC_{(0-tau)}$, apparent systemic clearance and apparent volume of distribution for ATV and DRV. Intensive pharmacokinetic assessments at steady state evaluating ATV, DRV, and COBI exposures should be obtained in a minimum of 54 subjects (divided into 4 age cohorts for ATV/COBI and divided into 3 age cohorts for DRV/COBI: 12 to less than 18 years, 6 to less than 12 years, 3 to less than 6 years, and 3 months to less than 3 years [ATV/COBI only]). Part A intensive pharmacokinetic sampling should be obtained in two parts: a) on or about Day -1 after multiple dosing of ATV/RTV or DRV/RTV and b) on or about Day 10 after multiple dosing of ATV/COBI or DRV/COBI. A summary of the results of the pharmacokinetic analyses should be provided to the Agency prior to initiation of Part B. Dose selection must be agreed upon with the FDA prior to initiating Part B. Sparse sampling for COBI, ATV and DRV must be obtained at multiple visits in all subjects during Part B of the study. PK samples in Part B (after Day 10) of the study will be collected at Weeks 12, 24, and 48 for subjects enrolled in both Part A and Part B and Weeks 4, 12, 24, 32, and 48 for subjects enrolled in Part B only.

The ATV and DRV exposures achieved when coadministered with COBI in pediatric patients must be similar to the exposures of ATV and DRV found to be safe and effective in adults when coadministered with RTV and should not be lower than any approved pediatric ATV/RTV or DRV/RTV regimen in any population.

- *Pharmacokinetic/Pharmacodynamic Endpoints:*

The pharmacokinetic and pharmacodynamic endpoints for Study 1 must be combined to explore the exposure-response for safety and effectiveness endpoints. The goals of this analysis are: a) to provide supportive evidence of antiviral activity; and b) to support the dosing recommendations. Safety and antiviral

activity assessments should include all the endpoints listed below, as well as ATV or DRV exposures (e.g., C_{tau} , $AUC_{0-24\text{h}}$, C_{max} , etc.), COBI exposure (e.g., C_{tau} , $AUC_{0-24\text{h}}$, C_{max} , etc.), and virologic failure. Clinical assessments will be obtained, including at baseline (Day 1), Day 10, and weeks 4, 8, 12, 16, 24, 32, 40, 48, and every 12 weeks thereafter.

▪ *Efficacy Endpoints:*

- The primary efficacy (antiviral activity) endpoint will be the proportion of subjects with HIV-1 RNA <50 copies/mL at Weeks 12, 24 and 48 as measured by sensitive PCR assay.
- Important secondary endpoints must include CD4+ cell counts (cells/mm³ and percentage) at Weeks 24 and 48, and change from baseline to Weeks 24 and 48 in HIV-1 RNA copies/mL.

▪ *Safety Endpoints:*

- Safety outcomes must include: reporting of clinical adverse events, tolerability, vital signs, clinical laboratory parameters, and growth parameters (height and weight).
- The following adverse events or laboratory abnormalities must be actively monitored: renal adverse events, elevation in ALT/AST and bilirubin (hepatotoxicity), rash, and clinically significant drug-drug interactions. All adverse events or laboratory abnormalities must be monitored until symptom resolution or until the condition stabilizes.
- Resistance: Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates prior to study enrollment, if available, and during treatment from pediatric subjects receiving ATV/COBI and DRV/COBI, particularly from those who experience loss of virologic response.
- A Data Monitoring Committee (DMC) must be included because:
 - of the possibility of serious toxicity with ATV/COBI and DRV/COBI, and
 - the study is being performed in children, a vulnerable population

See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees*,

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>

• *Known drug safety concerns and monitoring:*

1. Potential for clinically significant drug-drug interactions.

2. Cobicistat-induced increase in serum creatinine (inhibition of secretion in renal tubule) and renal adverse events.
3. Development of resistance substitutions in HIV-1.

A minimum of 100 pediatric subjects distributed across the age range to be studied will be required for the safety evaluation.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.
- *Drug information:*
 - *dosage form:* oral tablets and/or other age-appropriate formulations
 - *route of administration:* oral
 - *regimen:* once daily

Use an age-appropriate formulation in the study described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must

be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

Descriptive analyses of multiple-dose pharmacokinetics, safety and activity data in HIV-1-infected pediatric subjects is required. The trial must include an adequate number of subjects to characterize pharmacokinetics for dose selection. In addition, the study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance for ATV and DRV when coadministered with COBI in the following age groups, minimum numbers in parentheses:

- 12 years to < 18 years (ATV $n \geq 8$, DRV $n \geq 6$)
- 6 years to < 12 years (ATV $n \geq 8$, DRV $n \geq 6$)
- 3 years to < 6 years (ATV $n \geq 8$, DRV $n \geq 6$)
- 3 months to < 3 years (ATV $n \geq 12$ subjects, DRV not indicated in this age group)

Final selection of sample size for each age group must take into account all potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary in order to maintain the statistical power as stated above for adequate characterization of pharmacokinetics across the intended age range.

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrates that cobicistat is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you

should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the FDA website at <http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 15, 2019. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.
- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Stacey Min, Regulatory Project Manager, at 301-796-4253.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D.
Director
Office of Antiviral Products
Center for Drug Evaluation and Research

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

/s/

EDWARD M COX
03/27/2014

From: Hong, Myung-Joo P.
To: [Perna Menon \(Perna.Menon@gilead.com\)](mailto:Perna.Menon@gilead.com); "[Christophe Beraud](#)"
Subject: NDA 203093 & 203094.Advices
Date: Monday, March 24, 2014 12:05:00 PM

Dear Perna and Christophe, we have the following comment/request for EVG and COBI's Re-Submission:

"In NDA 205834 for Ledipasvir and Sofosbuvir tablets, where developmental methods were used in the batch analysis of ledipasvir drug substance, the specific methods were identified (Table 7 in S.4.4). Additionally, those methods and validation results were described in the NDA (S.7.3) together with bridging studies where appropriate. This approach could be very useful when the Cobicistat and Elvitegravir NDAs are resubmitted. It could also be useful to include in those resubmissions a summary of what was done as part of the supplemental validation listed for some methods in Gilead's February 21, 2014 letter."

Best Regards,

Pat

Myung-Joo Patricia Hong, M.S.

Senior Regulatory Health Project Manager

FDA/CDER/OAP/DAVP

10903 New Hampshire Ave

Bldg # 22, Room 6235

Silver Spring, MD 20993-0002

' 301-796-0807

' 301-796-9883 (fax)

✉ myung-joo.hong@fda.hhs.gov

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

/s/

MYUNG JOO P HONG
03/24/2014



NDA 203093
NDA 203094/Original 1
NDA 203094/Original 2

MEETING MINUTES

Gilead Sciences, Incorporated
Attention: Perna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitekta[®] (elvitegravir) tablets, 85 and 150 mg, and Tybost[®] (cobicistat) tablets, 150 mg.

We also refer to the teleconference between representatives of your firm and the FDA on January 22, 2014. The purpose of the teleconference was to present and discuss Gilead's proposal to address the comments in the Complete Response Letter for Vitekta[®] (elvitegravir) tablets and Tybost[®] (cobicistat) tablets.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Myung-Joo Patricia Hong, Regulatory Project Manager at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Other

Meeting Date and Time: January 22, 2014, 1 – 2 PM
Meeting Location: Teleconference

Application Number: NDA 203093
NDA 203094/Original 1
NDA 203094/Original 2

Product Name: Vitekta[®] (elvitegravir) and Tybost[®] (cobicistat)

Indication: Vitekta[®] (elvitegravir) for the treatment of HIV-1 infection and Tybost[®] (cobicistat) as a CYP3A inhibitor to increase systemic exposures of the HIV-1 protease inhibitors atazanavir and darunavir

Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Recorder: Myung-Joo Patricia Hong, M.S., Regulatory Project Manager

FDA ATTENDEES

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Linda Lewis, M.D., Clinical Team Leader, Division of Antiviral Products
Kimberly Struble, PharmD, Clinical Team Leader, Division of Antiviral Products
Peter Miele, M.D., M.P.H., Clinical Reviewer, Division of Antiviral Products
Russell Fleischer, MPH, PA-C, Clinical Reviewer, Division of Antiviral Products
Sarita Boyd, Pharm.D., Clinical Reviewer, Division of Antiviral Product
Peyton Myers, Ph.D., Nonclinical Reviewer, Division of Antiviral Products
Takashi Komatsu, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
Shirley Seo, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4
Islam Younis, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4
Rapti Madurawe, Ph.D., Product Branch Chief, DNDQA II
Stephen Miller, Ph.D., Product Team Leader, DNDQA II
Mahesh Ramanadham, Compliance Officer, OMPQ/DGMPA

Krishna Ghosh, Ph.D., Compliance Officer, OMPQ/DGMPA
Elizabeth Thompson, M.S., Chief Project Management Staff, Division of Antiviral Products
Karen Winestock, Chief Project Management Staff, Division of Antiviral Products
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager, Division of Antiviral Products

SPONSOR ATTENDEES

Reza Oliyai, Ph.D., VP, Formulation and Process Development
Taiyin Yang, Ph.D., SVP, Pharmaceutical Development and Manufacturing
Tammis Matzinger, VP, Quality Assurance
Gary Visor, Ph.D., VP, Analytical Operations
Javier Szwarcberg, M.D., MPH., Senior Director, Clinical Research
Joseph Custodio, Ph.D, Clinical Pharmacologist II, Clinical Pharmacology
Naomi Kautz, M.Sc., Sr. Manager, Regulatory Affairs

BACKGROUND

Gilead is developing Vitekta[®] (elvitegravir, EVG) tablets and Tybost[®] tablets (cobicistat, COBI). Vitekta[®] and Tybost[®] are part of Stribild[®] (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) single tablet regimen for the treatment of HIV-1 infection.

Vitekta[®] (EVG), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor, coadministered with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Tybost[®] (COBI) is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir (Original 1) and darunavir (Original 2) in the treatment of HIV-1 infection in adults.

The New Drug Applications for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094) were received on June 27 and 28, 2012, respectively. On April 15, 2013, DAVP requested that the NDA 203094 be separated into NDA 203094/Original 1 (indication of Tybost[®] as a pharmacoenhancer of atazanavir) and NDA 203094/Original 2 (indication of Tybost[®] as a pharmacoenhancer of darunavir). On April 26, 2014, Complete Response Letters for both products were issued due to the results of facility inspection findings at Gilead Sciences, Inc. located in Foster City, CA.

This Type A meeting was scheduled to discuss Gilead's proposal to address the comments in the Complete Response letters for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094/Original 1 and Original 2). Gilead Sciences sought agreement on:

- Gilead's proposal to address the deficiencies identified in facility inspections of the Gilead Foster City facility.

- Adequacy of data submitted in the responses to (b) (4) District Office to address the deficiencies identified for product quality for NDA 203093 and NDA 203094.
- Adequacy of the data provided to address the clinical pharmacology items in the Complete Response Letter for NDA 203094/Original 2.
- The indication for Tybost[®] (cobicistat) tablets can be expanded to include the use with darunavir in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined to NDA 203094.

The proposed resubmission for both products is targeted for March, 2014.

1.0 DISCUSSION

On January 16, 2014 the Division of Antiviral Products (DAVP) sent preliminary responses to questions the sponsor submitted in the meeting briefing package via electronic mail. After reviewing the Division's responses, Gilead decided to limit the meeting's discussion to Question 1 (Facility Inspections and Product Quality). Gilead provided slides in advance of the teleconference.

Gilead's questions are in **bold**, DAVP's preliminary responses are in *italicized font*; and the meeting discussions are in standard font.

1.1 Facility Inspections and Product Quality

Q 1: Gilead intends to include the method validation and bridging study reports for those analytical methods used during clinical development for release and stability testing of elvitegravir and cobicistat on silicon dioxide drug substances and Vitekta and Tybost drug products in DMF 25187, DMF 25188, NDA 203093 and NDA 203094, respectively. Does the Agency agree that the integrity of the drug substance and drug product release and stability data has been demonstrated and that the Quality issues identified in the Complete Response letters have been addressed satisfactorily so that Gilead may proceed with resubmission of the NDAs for Vitekta Tablets and Tybost Tablets?

The integrity of the data associated with the analytical method validation and method comparability studies appears to be adequate; however, the final determination can only be made during the review of the application. The integrity of this data will also be assessed during an on-site inspection. The most recent inspection of the Gilead Foster City site remains under review and the final status will be communicated through the (b) (4) district office.

Additionally, we refer to the teleconference held between CDER and Gilead on October 29, 2013 in which Gilead stated its intent to contract a third party expert to assist in the evaluation of the stability and testing program at Gilead Foster City. We request the current status of these efforts and clarification if the data used to support elvitegravir and cobicistat have undergone this evaluation.

Discussion: The discussion began with a presentation by Gilead.

Gilead presented the status of the third party (b) (4) expert evaluation of the stability and testing program and data at the Gilead Sciences, Foster City site. The main points from the presentation were: 1) Gilead has retained (b) (4) to assist in the evaluation of the 483 deficiencies and Gilead's corrective action plans to address issues identified by FDA during past inspections, as well as improvement plans for the stability and testing program at the Foster City site; 2) (b) (4) experts conducted independent audits of the analytical data generated at Gilead Foster City submitted in recent NDAs, including IDELA (idelalisib) (filed Sept 2013) and the upcoming NDA for sofosbuvir/ledipasvir (SOF /LDV) (1st Q2014 NDA filing planned) (see Attachment 1, slides 3 and 4 for (b) (4) assessment of the data submitted to support these two NDAs); and 3) the third party expert assessments will continue for future Gilead NDAs. Gilead plans to conduct similar audits for the analytical data that will support the resubmission of Vitekta and Tybost NDAs.

FDA inquired whether the Gilead Foster City site will be included as a testing site for resubmission of Vitekta and Tybost NDAs and whether the (b) (4) audit reports and certification will be provided for the analytical data sets generated at the site. Gilead stated that the most recent inspection was completed in (b) (4) 2013 and they plan to include data from the (b) (4) audit in the resubmission of the Vitekta and Tybost NDAs, along with updated stability data. The certificates of the integrity of the analytical data generated at the Gilead Foster City site have been drafted and will be included in the resubmission of the Vitekta and Tybost NDAs. FDA informed Gilead that an internal review of the (b) (4) 2013 inspection is on-going.

FDA emphasized that for the resubmissions, clear delineation should be made between analytical data generated at the Gilead Foster City site and analytical data generated by third-party contract laboratories.

FDA inquired about development methods and final methods/commercial methods and asked if Gilead had conducted any bridging studies between methods. Gilead responded that they had conducted a bridging study and submitted the results in response to the 483 observations. FDA stated that Gilead should include a reference guide to the batch analysis data and the linkage to the different methods (development methods versus final methods/commercial methods) with supportive validation and bridging data. Gilead stated it will include certifications and assessment results in the resubmission of Vitekta and Tybost NDAs.

FDA stated that Gilead had submitted this information early in the sofosbuvir development process, which provided FDA with a reasonable depth of evaluation. It would be helpful for all three applications (EVG, COBI, and SOF/LDV) to submit information about data generated using developmental methods.

FDA asked Gilead to clarify the role of the Foster City site in the resubmission of the two NDAs. FDA noted that the initial data for Vitekta and Tybost were generated at the Foster City site and asked about data generated at other sites. Gilead stated the Foster City site is a key site for drug development methodology and that quality control (QC) release testing at the site had been re-qualified. For upcoming applications, Gilead plans to use alternative facilities for commercial testing. For IDELA, (b) (4) will be used as a commercial testing site and (b) (4) is a contract laboratory for other projects. Gilead offered to submit a list of contractors. Gilead noted that there are redundancies for commercial analytical testing facilities for all three NDAs (COBI, EVG, and SOS/LDV) and its general qualification strategy includes multiple manufacturing sites and multiple contract testing laboratories along with the Foster City site. FDA asked Gilead to submit any redundancies in testing facilities. Gilead agreed to submit the requested information with the upcoming NDA and resubmission of the Vitekta and Tybost NDAs.

1.2 Clinical Pharmacology for NDA 203094/Original 2 (Tybost)

Q2: Does the Agency agree that the clinical pharmacology information provided in the Meeting Information Package adequately addresses the 483 observations at the (b) (4) laboratories so that Gilead could proceed with resubmission of NDA 203094?

Plases see our response below for Q2 and Q3.

Q3: Does the Agency agree that the indication of COBI can be expanded to include increase in systemic exposure of darunavir (DRV) in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined into a single NDA 203094?

Overall, the clinical pharmacology information included in the meeting package to address the 483 observations from the inspections of the (b) (4) bioanalytical laboratories is sufficient to proceed with the resubmission of NDA 203094.

There is only one NDA for cobicistat, NDA 203094. However, the NDA has two original submissions. To reactivate the review clock for NDA 203094 Original 1 and Original 2, you will need to submit a resubmission to both. This can be accomplished by submitting all of the data to Original 2 and a cross reference letter, all required administrative forms, and SPL labeling to Original 1. The labeling (package insert and Patient

Information) for atazanavir/cobicistat and darunavir/cobicistat should be merged and submitted to both submissions.

Discussion: The sponsor accepted DAVP's response; no discussion occurred.

The following comments were included in our preliminary responses:

- 1. In the darunavir/ritonavir method validation report (Amendment 1), the retest date for the certificate of analysis for the cobicistat reference standard was (b) (4). However, the analytical experiments for Amendment 1 were conducted up through June 25, 2013. Please specify whether the cobicistat reference standard with a retest date of (b) (4) was recertified and, if the reference standard was recertified, please provide the updated certificate of analysis. If the reference standard was not recertified, please provide information to support the acceptability of the stability results for darunavir combined with cobicistat from runs 9 to 10 that were conducted after (b) (4).*
- 2. In Table 2 of the meeting package, please clarify how the data from (b) (4) for Subject 2029 was handled. Was the pre-dose concentration from Period 1 excluded or assigned a value of below the limit of quantification (BLQ)?*
- 3. Please provide further information regarding the storage conditions for the darunavir and ritonavir plasma samples (b) (4). Specifically, were the plasma samples that were analyzed for darunavir and ritonavir concentrations stored at (b) (4)?*
- 4. Please specify whether QCs or calibration standards prepared on the day of the stability assessment (b) (4) for the long term stability assessments) were included as part of (b) (4) that were conducted as part of the darunavir/ritonavir method validation (Amendment 1).*
- 5. As part of the resubmission for NDA 203094, please submit both the original and the revised pharmacokinetic datasets that were used in deriving Table 1 and Table 2 of the meeting package in SAS transport (.xpt) format and include information that outlines the differences between the two datasets.*
- 6. DAVP recommends that you conduct a relative bioavailability study to compare elvitegravir exposures following administration of elvitegravir and cobicistat as single entities versus administration of elvitegravir and cobicistat as components of the Stribild[®] fixed-dose combination tablet. (b) (4)*

Discussion: The sponsor accepted DAVP's comments; no discussion occurred.

2.0 ADDITIONAL POST-MEETING COMMENTS

- Comprehensive third party audit reports are not required in the resubmission of these NDAs. Copies of the third party audit reports can be communicated to the district office, who will then communicate with CDER as needed.
- FDA requests that Gilead confirm that the (b) (4) review of data relevant to the three applications will be completed before each application is submitted (SOF/LDV) or resubmitted (COBI or EVG).

3.0 ATTACHMENTS AND HANDOUTS

- Copy of Gilead's presentation slides

5 Pages have been Withheld in Full as B4(CCI/TS) Immediately
Following this Page

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

/s/

DEBRA B BIRNKRANT
02/11/2014



NDA 203093
NDA 203094/Original 1
NDA 203094/Original 2

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Incorporated
Attention: Perna Menon, Ph.D.
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Menon:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitekta[®] (elvitegravir) tablets, 85 and 150 mg and Tybost[®] (cobicistat) tablets, 150 mg.

We also refer to your December 13, 2013, correspondence requesting a meeting to present and discuss Gilead's proposal to address the comments in the Complete Response Letter for Vitekta[®] (elvitegravir) tablets and Tybost[®] (cobicistat) tablets.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: Other

Meeting Date and Time: January 22, 2014, 1 – 2 PM
Meeting Location: WO Bldg 22, Room 1315

Application Number: NDA 203-093
NDA 203-094/Original 1
NDA 203-094/Original 2

Product Name: Vitekta[®] (elvitegravir) and Tybost[®] (cobicistat)

Indication: Vitekta[®] (elvitegravir) for the treatment of HIV-1 infection and Tybost[®] (cobicistat) as a CYP3A inhibitor to increase systemic exposures of the HIV-1 protease inhibitors atazanavir and darunavir

Sponsor/Applicant Name: Gilead Science, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 22, 2014, 1 - 2 PM, WO Bldg 22, Room 1315 between Gilead Sciences, Inc. and the Division of Antiviral Products (DAVP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Gilead is developing Vitekta[®] (elvitegravir, EVG) tablets and Tybost[®] tablets (cobicistat, COBI). Vitekta[®] and Tybost[®] are part of Stribild[®] (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) single tablet regimen for the treatment of HIV-1 infection.

Vitekta[®] (EVG), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor, coadministered with a protease inhibitor/ritonavir and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Tybost[®] (COBI) is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir (Original 1) and darunavir (Original 2) in the treatment of HIV-1 infection in adults.

The New Drug Applications for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094) were received on June 27 and 28, 2012, respectively. On April 15, 2013, DAVP requested that the NDA 203094 be separated into NDA 203094/Original 1 (indication of Tybost[®] as a pharmacoenhancer of atazanavir) and NDA 203094/Original 2 (indication of Tybost[®] as a pharmacoenhancer of darunavir). On April 26, 2014, Complete Response Letters for both products were issued due to the results of facility inspection findings in Gilead Sciences, Inc. located in Foster City, CA.

This Type A meeting was scheduled to present and discuss Gilead's proposal to address the comments in the Complete Response letters for Vitekta[®] (NDA 203093) and Tybost[®] (NDA 203094/Original 1 and Original 2). Gilead Sciences seeks agreement on:

- Gilead's proposal to address the deficiencies identified in facility inspections of the Gilead Foster City facility.
- Adequacy of data submitted in the responses to [REDACTED]^{(b) (4)} District Office to address the deficiencies identified for product quality for NDA 203093 and NDA 203094.
- Adequacy of the data provided to address the clinical pharmacology items in the Complete Response Letter for NDA 203094/Original 2.
- The indication for Tybost[®] (cobicistat) tablets can be expanded to include the use with darunavir in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined to NDA 203094.

2.0 DISCUSSION

Gilead's questions are in bold italics and DAVP comments are in standard font.

2.1 Facility Inspections and Product Quality

Q 1: Gilead intends to include the method validation and bridging study reports for those analytical methods used during clinical development for release and stability testing of elvitegravir and cobicistat on silicon dioxide drug substances and Vitekta and Tybost drug products in DMF 25187, DMF 25188, NDA 203093 and NDA 203094, respectively. Does the Agency agree that the integrity of the drug substance and drug product release and stability data has been demonstrated and that the Quality issues identified in the Complete Response letters have been addressed satisfactorily so that Gilead may proceed with resubmission of the NDAs for Vitekta Tablets and Tybost Tablets?

The integrity of the data associated with the analytical method validation and method comparability studies appears to be adequate; however, the final determination can only be made during the review of the application. The integrity of this data will also be assessed during an on-site inspection. The most recent inspection of the Gilead Foster City site remains under review and the final status will be communicated through the (b) (4) district office.

Additionally, we refer to the teleconference held between CDER and Gilead on October 29th, 2013 in which Gilead stated its intent to contract a third party expert to assist in the evaluation of the stability and testing program at Gilead Foster City. We request the current status of these efforts and clarification if the data used to support elvitegravir and cobicistat have undergone this evaluation.

2.2 Clinical Pharmacology for NDA 203094/Original 2 (Tybost)

Q2: Does the Agency agree that the clinical pharmacology information provided in the Meeting Information Package adequately addresses the 483 observations at the (b) (4) so that Gilead could proceed with resubmission of NDA 203094?

Please see our response below for Q2 and Q3.

Q3: Does the Agency agree that the indication of COBI can be expanded to include increase in systemic exposure of darunavir (DRV) in the treatment of HIV-1 infection and administratively allow the NDA 203094/Original 1 and Original 2 to be combined into a single NDA 203094?

Overall, the clinical pharmacology information included in the meeting package to address the 483 observations from the inspections of the (b) (4) bioanalytical laboratories is sufficient to proceed with the resubmission of NDA 203094.

There is only one NDA for cobicistat, NDA 203094. However, the NDA has two original submissions. To reactivate the review clock for NDA 203094 Original 1 and Original 2, you will need to submit a resubmission to both. This can be accomplished by submitting all of the data to Original 2 and a cross reference letter, all required administrative forms, and SPL labeling to Original 1. The labeling (package insert and Patient information) for atazanavir/cobicistat and darunavir/cobicistat should be merged and submitted to both submissions.

We have the following additional comments:

1. In the darunavir/ritonavir method validation report (Amendment 1), the retest date for the certificate of analysis for the cobicistat reference standard was (b) (4). However, the analytical experiments for Amendment 1 were conducted up through June 25, 2013. Please specify whether the cobicistat reference standard with a retest date of (b) (4) was recertified and, if the reference standard was recertified, please provide the updated certificate of analysis. If the reference standard was not recertified, please provide information to support the acceptability of the stability results for darunavir combined with cobicistat from (b) (4) that were conducted after (b) (4).
2. In Table 2 of the meeting package, please clarify how the data from (b) (4) for Subject 2029 was handled. Was the pre-dose concentration from Period 1 excluded or assigned a value of below the limit of quantification (BLQ)?
3. Please provide further information regarding the storage conditions for the darunavir and ritonavir plasma samples at (b) (4). Specifically, were the plasma samples that were analyzed for darunavir and ritonavir concentrations stored at (b) (4)?
4. Please specify whether QCs or calibration standards prepared on the day of the stability assessment ((b) (4) for the long term stability assessments) were included as part of (b) (4) that were conducted as part of the darunavir/ritonavir method validation (Amendment 1).
5. As part of the resubmission for NDA 203094, please submit both the original and the revised pharmacokinetic datasets that were used in deriving Table 1 and Table 2 of the meeting package in SAS transport (.xpt) format and include information that outlines the differences between the two datasets.
6. DAVP recommends that you conduct a relative bioavailability study to compare elvitegravir exposures following administration of elvitegravir and cobicistat as

single entities versus administration of elvitegravir and cobicistat as components of the Stribild[®] fixed-dose combination tablet. (b) (4)

(b) (4)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

As your original Pediatric Plans for elvitegravir and cobicistat were submitted with the original NDAs, you may reference those plans in your resubmissions if no substantive changes are proposed. Please provide an update of any changes to the original Pediatric Plans including anticipated timelines.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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/s/

MYUNG JOO P HONG
01/16/2014



NDA 203094/Original 1
NDA 203094/Original 2

MEETING REQUEST GRANTED

Gilead Sciences, Incorporated
Attention: Naomi Kautz, M.S.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Kautz:

Please refer to your New Drug Application (NDA) dated June 26, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tybost™ (cobicistat) tablets, 150 mg.

We also refer to your December 13, 2013, correspondence requesting a meeting to present and discuss Gilead's proposal to address the comments in the Complete Response Letter for Tybost™ (cobicistat) tablets. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: January 22, 2014
Time: 1 - 2 PM Eastern Time
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Invited CDER participants:

Division of Antiviral Products

Debra Birnkrant, M.D., Division Director
Jeffrey Murray, M.D., Deputy Director
Kendall Marcus, M.D., Deputy Director for Safety
Linda Lewis, M.D., Clinical Team Leader
Kimberly Struble, Pharm.D., Clinical Team Leader
Russell Fleischer, M.P.H., PA-C., Clinical Reviewer
Peter Miele, M.D., Clinical Reviewer
Sarita Boyd, M.D., Clinical Reviewer

Julian O'Rear, Ph.D., Clinical Virology Team Leader
Sung Rhee, Ph.D., Clinical Virology Reviewer
Takashi Komatsu, Ph.D., Clinical Virology Reviewer
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader
Peyton Myers, Ph.D., Pharmacology/Toxicology Reviewer
Pritam Verma, Ph.D., Pharmacology/Toxicology Reviewer
Beth Thompson, M.S., Chief Regulatory Project Management
Karen Winestock, Chief Regulatory Project Management
Myung-Joo Patricia Hong, M.S., Regulatory Project Management

Office of Clinical Pharmacology

Shirley Seo, Ph.D., Clinical Pharmacology Team Leader, Division of
Clinical Pharmacology 4
Islam Younis, Pharm.D., Clinical Pharmacology Team Leader,
Division of Clinical Pharmacology 4
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, Division of
Clinical Pharmacology 4
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer, Division of
Clinical Pharmacology 4
Jeffrey Florian, Pharm.D., Pharmacometrics Team Leader, Division of
Clinical Pharmacology 4

Office of New Drug Quality Assessment

Rapti Madurawe, Ph.D., Product Branch Chief, DNDQA II
Stephen Miller, Ph.D., Product Team Leader, DNDQA II
Fugiang Liu, Ph.D., Product Reviewer, DNDQA II
Milton Sloan, Ph.D., Product Reviewer, DNDQA II
Karen Riviere, Ph.D., Biopharmaceutics Reviewer, DNDQA II
Deepika Arora Lakhani, Ph.D., Biopharmaceutics Reviewer, DNDQA III

Office of Compliance

Krishnakali Ghosh, Compliance Officer, OMPQ/DGMPA
Tara Goen, Compliance Officer, OMPQ/DGMPA
Mahesh Ramanadham, Compliance Officer, OMPQ/DGMPA

Office of Biometrics

Greg Soon, Ph.D., Biometrics Team Leader, OB/DBIV
Yanming Yin, Ph.D., Biometrics Reviewer, OB/DBIV

Please e-mail me any updates to your attendees at myung-joo.hong@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign

Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Myung-Joo Patricia Hong at 301-796-0807; or Michael Stanfield at 301-796-1500.

If you have any questions, call me at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	January 22, 2014: 1 PM
MEETING ENDING DATE AND TIME	January 22, 2014: 2 PM
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO Bldg 22, Room 1315
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Myung-Joo Patricia Hong Regulatory Project Manager WO Bldg 22, Room 6235 301-796-0807
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MYUNG JOO P HONG
12/17/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2013

To: Naomi Kautz, M.Sc. Senior Manager, Regulatory Affairs	From: Stacey Min, Pharm.D. Division of Antiviral Products
Company: Gilead Sciences, Inc.	Title: Regulatory Project Manager
Fax number: 650-522-5489	Fax number: 301-796-9883
Phone number: 650-522-2789	Phone number: 301-796-4253

Subject: NDA 203094 and NDA 203093 Comments on safety update for resubmission

Total number of pages including cover: 3

Comments:

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MEMORANDUM OF FACSIMILE:

Date: September 17, 2013

NDA: 203094
203093

Drug: TYBOST (cobicistat)
VITEKTA (elvitegravir)

To: Naomi Kautz, M.Sc., Senior Manager, Regulatory Affairs
Perena Menon, Ph.D., Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Stacey Min, Pharm.D., Senior Regulatory Project Manager and
Pat Hong, M.S., Senior Regulatory Project Manager

Subject: NDA 203094 and NDA 203093 Comments on Proposed Safety
Update for Resubmission

Please refer to your NDA 203094 for TYBOST (cobicistat) and NDA 203093 for VITEKTA (elvitegravir). We also refer to your August 13, 2013 submission to both the NDAs requesting feedback on your proposed safety update for your resubmission for cobicistat and elvitegravir. We have reviewed your submission agree that your proposal is acceptable if you follow the same format as the original Safety Update, including a summary of new data since the original NDA submission. Please confirm that the trials being included are similar to those in the Safety Update for the original NDA submission.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

STACEY MIN
09/17/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2013

To: Naomi Kautz, M.Sc. Senior Manager, Regulatory Affairs	From: Stacey Min, Pharm.D. Division of Antiviral Products
Company: Gilead Sciences, Inc.	Title: Regulatory Project Manager
Fax number: 650-522-5489	Fax number: 301-796-9883
Phone number: 650-522-2789	Phone number: 301-796-4253
Subject: NDA 203094 Clinical Pharmacology Comments	

Total number of pages including cover: 4

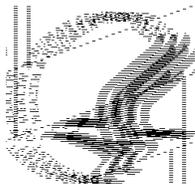
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MEMORANDUM OF FACSIMILE:

Date: July 15, 2013
NDA: 203094
Drug: TYBOST (cobicistat)
To: Naomi Kautz, M.Sc., Senior Manager, Regulatory Affairs
Sponsor: Gilead Sciences, Inc.
From: Stacey Min, Pharm.D., Senior Regulatory Project Manager
Subject: NDA 203094 Clinical Pharmacology Comments

Please refer to your NDA 203094 for TYBOST (cobicistat). We also refer to our April 11, 2013, comments consisting of PMRs for cobicistat in combination with atazanavir and for cobicistat in combination with darunavir. This correspondence also included our comments on OSI inspections. Lastly, we refer to your April 15, 2013, response to our April 11, 2013 correspondence.

As a follow up to the comments April 11, 2013 comments, FDA would like to clarify the following:

1. For comment #2 that requested an updated summary of darunavir pharmacokinetic parameters and statistical analysis for the GS-US-216-115 trial, please provide an updated analysis with all the changes included (a, b, and c) combined in one reanalysis summary for the GS-US-216-115 trial.
2. For comment #3 that requested an updated summary of cobicistat pharmacokinetic parameters and statistical analysis for the GS-US-216-116 trial, please provide an updated analysis with all the changes included (exclusion of data from both run 18 and run 22) combined in one reanalysis summary for the GS-US-216-116 trial.

These updated analyses should be submitted as part of the complete response for the cobicistat NDA that will be provided to the agency in the fourth quarter of 2013.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-4253 if you have any questions regarding the contents of this transmission.

Stacey Min, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

STACEY MIN
07/15/2013



MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2013
TIME: 3:30 - 4 pm
LOCATION: White Oak Bldg 22, Room 6201
APPLICATION: NDA 203093 & 203094
DRUG NAME: Vitakta™ and Tybost™
TYPE OF MEETING: Informal Advice - Teleconference

Meeting Recorder: Myung-Joo Patricia Hong, M.S., Regulatory Project Manager

FDA ATTENDEES:

Debra Birnkrant, M.D., Division Director, DAVP
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Linda Lewis, M.D., Clinical Team Leader, DAVP
Russ Fleischer, PA-C, MPH, Clinical Reviewer (via phone)
Kim Struble, Pharm.D., Clinical Team Leader (via phone)
Peter Miele, M.D., Clinical Reviewer (via phone)
Rapti Madurawe, Ph.D., CMC Branch Chief, ONDQA
Stephen Miller, Ph.D., CMC Team Leader, ONDQA
Celia Cruz, Ph.D., CMC Reviewer, ONDQA
Milton Sloan, Ph.D., CMC Reviewer, ONDQA (via phone)
Fugiang Liu, Ph.D., CMC Reviewer, ONDQA (via phone)
Kareen Rieviere, Ph.D., CMC Reviewer, ONDQA
Deepika Arora Lakhani, Ph.D., CMC Reviewer, ONDQA (via Phone)
Krishnakali Ghosh, Ph.D., Compliance Officer, GDMAB (via phone)
Tara Goen, Acting Branch Chief, NDMAB, Office of Compliance
Madesh Ramanadham, NDMAB, Office of Compliance
Karen Winestock, Chief Project Management Staff
Beth Thompson, M.S., Acting Chief Project Management Staff
Abiola Olagundoye-Alawode, Pharm.D., Regulatory Project Manager
Sammie Beam, Regulatory Project Manager
Myung-Joo Patricia Hong, M.S., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES (Gilead's participants):

Andrew Cheng, M.D., Ph.D., Senior Vice President, Clinical Research
Javier Szwarcberg, M.D., Senior Director, Clinical Research
David Pizzuti, M.D., Vice President, Regulatory Affairs
Paul Tomkins, Ph.D., Senior Director, Regulatory Affairs
Christophe Beraud, Ph.D., Director, Regulatory Affairs
Taiyin Yang, Ph.D., Senior Vice President, Pharmaceutical Development and Manufacturing

Ron Branning, B.B.A., Vice President, Quality Assurance
Sujatha Narayan, M.S., Senior Director CMC, Regulatory Affairs

BACKGROUND:

Today, April 26, 2013, DAVP issued complete response letters for NDA 203093 (Vitekta™) and 203094 (Tybost™). A teleconference was scheduled to inform the applicant about the Division's action (Complete Response) and advise the applicant on how to resolve the issues identified during the inspection conducted at the Gilead Sciences (Foster City, CA) manufacturing facility site.

During the recent inspection of the Gilead Sciences (Foster City, CA) release and stability testing facility for these applications, FDA field investigators found significant deficiencies and discussed them with the firm management. FDA field investigators found significant concerns regarding the release and stability data presented in the NDAs and DMFs primarily due to lack of validation of the test methods used to obtain these data. The firm management acknowledged these deficiencies in their letter dated April 23, 2013. Satisfactory resolution of the significant deficiencies is required before this application may be approved.

DISCUSSION:

The Division of Antiviral Products (DAVP) initiated the discussion by acknowledging that this was a courtesy call related to the Complete Response Letters issued today. The DAVP commented that there were sufficient data from field inspection to issue a Complete Response letter. DAVP could not comment on all the deficiencies, as inspections were still ongoing, but noted that there was lack of validation of test methods used and the release/stability tests were not validated for both NDAs. Some deficiencies represented repeat observations noted as deficiencies during the previous STRIBILD application (NDA 203100). The DAVP and Office of Compliance recommended to Gilead Sciences the following:

1. Determine appropriate corrective actions to the Form FDA-483 issued to the firm and have the manufacturing facility submit a written response directly to the District Office.
2. Once Gilead has determined the extent/impact of the findings, submit detailed proposals to reconcile the analytical methods and resolve the deficiencies.
3. Request a Type A meeting (within 3 months) to discuss the impact of the findings on the data submitted in the application. The meeting request should be submitted to the review division.

The DAVP recommended that Gilead's follow-up action should be a priority and the firm should provide their responses as thoroughly as possible. The firm should provide adequate data to review and should submit a complete meeting package.

The DAVP reiterated that there are multiple deficiencies listed in the Form-483 and Gilead Sciences should consult the District Office to resolve the issues identified during inspection. The DAVP asked Gilead to determine how these findings will impact the new NDA (NDA 204671), which was submitted on April 8, 2013. Gilead Sciences committed to follow-up on this issue.

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
05/02/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: April 22, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover:

Comments: - Label /DHCP letter revisions/proposals

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: April 22, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) - **Label/ DHCP letter revisions/proposals**

Please refer to your New Drug Application (NDA) submitted June 26, 2012 for cobicistat 150 mg tablet.

The review team has made revisions/proposals to the Label and Dear Healthcare Provider (DHCP) Letter for Tybost (cobicistat).

The following comments are being conveyed on behalf of the review team for your application:

Find the attached cobicistat Label and Dear Healthcare Provider Letter which contains the review team's suggested revisions, comments, and rationale.

Please send your responses to the NDA (Orig-1) no later 10AM on Wednesday, April 24, 2013.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
04/22/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: April 16, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 52

Comments: - Label/PPI/DHCP letter revisions/proposals
- Clinical Pharmacology information request

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: April 16, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) - **Label/PPI/DHCP letter revisions/proposals**
- **Clinical Pharmacology information request**

Please refer to your New Drug Application (NDA) submitted June 26, 2012 for cobicistat 150 mg tablet.

The review team has made revisions/proposals to the Label, Patient Package Insert (PPI) and Dear Healthcare Provider (DHCP) Letter for Tybost (cobicistat).

The following comments are being conveyed on behalf of the review team for your application:

Find the attached cobicistat Label, PPI and Dear Healthcare Provider Letter which contains the review team's suggested revisions, comments, and rationale.

In order to preserve the formatting and font to the revised PPI, please make your changes directly to the attached PPI (WORD version would be sent separately).

Clinical Pharmacology

In vitro, pH dependent solubility effects were observed for cobicistat. Please provide additional information regarding the predicted impact of cobicistat pH dependent solubility effects on atazanavir or darunavir exposure with concomitant use.

Please send your responses to the NDA (Orig-1) no later than Thursday, April 18, 2013.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
04/16/2013



NDA 203094/Original 1
NDA 203094/Original 2

ADVICE

Gilead Sciences, Inc.
Attention: Naomi Kautz, MSc
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Kautz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tybost, cobicistat 150 mg tablet.

NDA 203094 provides for the use of Tybost, cobicistat 150 mg tablet for the following indications which, for administrative purposes, we have designated as follows:

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

All future submissions to your NDA should specify the NDA number and all Original numbers to which each submission pertains.

If you have any questions, call me at (301) 796-3982 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Abiola Olagundoye-Alawode, Pharm.D., RPh.
LCDR, USPHS
Regulatory Health Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
04/15/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: April 11, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 4

Comments: NDA 203094
- PREA PMR recommendation

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: April 11, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat)
- PREA **PMR recommendation**

Please refer your New Drug Application (NDA) 203094 submitted June 26, 2012 for cobicistat tablets.

Additional reference is made to the PMR recommendations and comments regarding OSI inspections that were conveyed to you today, April 11, 2013.

The following PREA PMR is recommended based on review of the current submission:

1. Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of once daily 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 pharmacokinetic (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 at least 24 weeks of dosing.

PMR Schedule Milestones:

Final Protocol Submission:

MM/YYYY

Study/Trial Completion:

MM/YYYY

Study Report Submission:

MM/YYYY

Please send your responses to the NDA no later than noon, Tuesday, April 16, 2013.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
04/11/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: April 11, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 6

Comments: NDA 203094
- PMC/PMR recommendations
- Comments regarding OSI inspections

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: April 11, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) -
- **PMC/PMR recommendations**
- **Comments regarding OSI inspections**

Please refer your New Drug Application (NDA) 203094 submitted June 26, 2012 for cobicistat tablets.

Additional reference is made to DAVP draft labeling recommendations that were conveyed to you on April 1, 2013 and to your response dated April 9, 2013.

The following PMRs are recommended based on review of the current submission:

Cobicistat in combination with atazanavir

1. **PMR-** Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progesterin components of a combined oral contraceptives.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Study/Trial Completion:	<u>MM/YYYY</u>
	Study Report Submission:	<u>MM/YYYY</u>

2. **PMR-** Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
--------------------------	----------------------------	----------------

Study/Trial Completion:	<u>MM/YYYY</u>
Study Report Submission:	<u>MM/YYYY</u>

- PMR-** Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Study/Trial Completion:	<u>MM/YYYY</u>
	Study Report Submission:	<u>MM/YYYY</u>

Cobicistat in combination with darunavir:

- PMR-** Conduct a clinical trial in healthy subjects 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 contraceptives.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Study/Trial Completion:	<u>MM/YYYY</u>
	Study Report Submission:	<u>MM/YYYY</u>

- PMR-** Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Study/Trial Completion:	<u>MM/YYYY</u>
	Study Report Submission:	<u>MM/YYYY</u>

- PMR-** Conduct a clinical trial in healthy subjects to evaluate the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Study/Trial Completion:	<u>MM/YYYY</u>
	Study Report Submission:	<u>MM/YYYY</u>

In addition, we have the following comments/requests regarding the cobicistat OSI inspections:

- Please provide information on the following issues for the long term stability experiments being conducted for darunavir (b) (4)

_____ :

_____ (b) (4)

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The above information will be used as a basis in preparation for the discussion at the teleconference meeting scheduled for April 11, 2013, 3:00 P.M. – 4:30 P.M, between Gilead Sciences, Inc. and the Division of Antiviral Products.

Please send your responses to the NDA no later than noon, Tuesday, April 16, 2013.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
04/11/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 203094

Drug: TYBOST (cobicistat) tablets

Date: April 1, 2013

To: Naomi Kautz, M.Sc., Senior Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S., Regulatory Project Manager, DAVP
for Abiola Olagundoye, Pharm.D., Regulatory Project Manager, DAVP

Subject: NDA 203094 – Revised labeling and Dear Healthcare Provider letter

Please refer to your New Drug Application (NDA) dated June 26, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tybost (cobicistat) tablets. We also refer to your submission of March 21, 2013, received March 22, 2013, in response to our labeling comments of March 12 and March 15, respectively.

The attached comments regarding the proposed Tybost prescribing information and the draft Dear Healthcare Provider letter are being conveyed to you on behalf of the review team. Note that comments on the Patient Information will be communicated at a later date.

Please submit your response by Tuesday, April 9, 2013.

Please contact Abiola Olagundoye at 301-796-3982 if you have any questions regarding the contents of this transmission.

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

Enclosed: Draft Prescribing Information and Draft Dear Healthcare Provider Letter

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/s/

KATHERINE SCHUMANN
04/01/2013

Executive CAC

Date of Meeting: February 19, 2013

Committee: David Jacobson Kram, Ph.D., D.A.B.T., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Abby Jacobs, Ph.D., OND IO, Member
Whitney Helms, PhD, DHOT, Alternate Member
Hanan Ghantous, Ph.D., D.A.B.T., DAVP, Pharm Tox Supervisor
L. Peyton Myers, Ph.D., DAVP, Presenting Reviewer

Author of Minutes: L. Peyton Myers, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 203-094

Drug Name: Cobicistat

Sponsor: Gilead Sciences

Background

Cobicistat (COBI, 150-mg) as a component of STRIBILD® (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), is an approved drug (NDA 203-100) for the treatment of human immunodeficiency virus-1 (HIV-1). In the current NDA (203-094), the Sponsor is seeking the approval of COBI as a single agent.

COBI inhibits human CYP3A4 with high affinity and is used with other anti-HIV drug substances that are CYP3A4 substrates, in order to increase the exposure of those drug substances. COBI itself has no antiviral activity. COBI is orally administered as a tablet at a concentration of 150 mg. COBI will be administered with other anti-retroviral agents.

TWO YEAR CARCINOGENICITY STUDY IN RATS

- Species/strain: Sprague Dawley rats/CRL
- Doses: daily doses of 0, 0, 10, 25, 50 (males); 0, 0, 5, 15, 30 (females)
- Vehicle: 95% propylene glycol (PG)/5% ethanol (EtOH) (v/v) (pH 2.3 ± 0.1)
- Route: Oral gavage
- Basis of dose selection: MTD and AUC

Executive CAC concurred with the dose selection.

(See Exec. CAC minutes from May 26, 2009)

Study findings

The number of surviving animals in the vehicle control groups reached 20 animals earlier than expected. Gilead contacted the Division on April 13, 2011 (week 89 of dosing) with the contingency plan for early termination. DAVP consulted the CAC and provided responses to Gilead on early termination on April 21, 2011.

Due to the early termination, males were dosed for a minimum of 97 weeks and females were dosed for a minimum of 102 weeks. Administration of GS-9350 did not have a negative impact on survival, and sufficient numbers of animals survived to adequately evaluate carcinogenicity.

AUC0-t hr values on Day 26 were between 1.8 and 2.1- fold of clinical exposure.

Nonneoplastic and neoplastic microscopic findings attributed to GS-9350 were limited to the thyroid and liver. Findings included: thyroid follicular cell adenoma M/F; thyroid follicular carcinoma, M only, thyroid follicular cell hypertrophy, M/F; centrilobular hepatocyte hypertrophy, M/F; karyocytomegaly, M/F.

These findings are considered secondary to the hepatic microsomal enzyme induction as well as thyroid hormone imbalance previously observed in repeat dose studies in rats with GS-9350.

Table 1 - Incidence of GS-9350-Related Neoplastic Findings in the Thyroid in the Rat

Sex	GS-9350									
	Males					Females				
Dose Level (mg/kg/day)	0 (water)	0 (vehicle)	10	25	50	0 (water)	0 (vehicle)	5	15	30
Thyroid										
Number Examined	65	65	65	65	65	65	65	65	65	65
B-Adenoma, Follicular Cell	3	0	1	5	15	0	0	0	2	6
M-Carcinoma, Follicular Cell	0	0	0	1	5	0	0	0	1	2
B-Adenoma and M-Carcinoma, Follicular Cell	3	0	1	6	20	0	0	0	3	7*

* Note: Sponsor identified 8 combined thyroid neoplasms. FDA statistical review identified 7. Both were statistically significant, but the discrepancy is noted here.

Table 2 - Incidence of GS-9350-Related Nonneoplastic Microscopic Findings in the Thyroid in the Rat

Sex	GS-9350									
	Males					Females				
Dose Level (mg/kg/day)	0 (water)	0 (vehicle)	10	25	50	0 (water)	0 (vehicle)	5	15	30
Thyroid										
Number Examined	65	65	65	65	65	65	65	65	65	65
Hypertrophy, Follicular Cell	5	1	3	17	25	1	1	3	9	16
Hyperplasia, Follicular Cell	3	2	3	3	5	0	0	1	4	4

Table 3 - Incidence of GS-9350-Related Nonneoplastic Microscopic Findings in the Liver in the Rat

Dose Level (mg/kg/day)	Sex	GS-9350									
		Males					Females				
		0 (water)	0 (vehicle)	10	25	50	0 (water)	0 (vehicle)	5	15	30
Liver	Number Examined	65	65	65	65	65	65	65	65	65	65
	Karyocytomegaly, Hepatocyte	1	0	1	8	13	4	3	3	7	8
	Hypertrophy, Hepatocyte, Centrilobular	6	5	16	25	27	1	0	0	0	12

Statistical evaluation

The FDA statistical analysis considered thyroid follicular cell adenomas and carcinomas (combined) in males and females increased according to trend and pairwise at the high dose.

TWO YEAR CARCINOGENICITY STUDY IN MICE

- Species/strain: Crl:CD-1(ICR) mice
- Doses: daily dosing of 0, 0, 5, 15, 50 (males) and 0, 0, 10, 30, 100
- Vehicle: multiple vehicles.
 - Day 1 -- Week 13: 95% propylene glycol (PG)/5% ethanol (EtOH) (v/v) (pH 2.3 ± 0.1)
 - Week 14-25: 95% PG/5% EtOH (v/v) (not pH-adjusted)
 - Week 26 – end of study: 10% PG in 90% 40 mM acetate buffer (v/v) (pH 4.0 ± 0.1)
- Route: Oral gavage
- Basis of dose selection: MTD and AUC ratio.

Executive CAC concurred with the dose selection.
(See Exec. CAC minutes from May 26, 2009.)

Study findings

The number of surviving animals in the vehicle control groups reached 20 animals earlier than expected. Gilead contacted the Division on December 20, 2010 (week 73 of dosing) with the contingency plan for early termination. DAVP consulted the CAC and subsequently requested follow up information (survival curves) from Gilead, which were provided on January 5, 2011. DAVP further consulted the CAC and provided responses to Gilead on early termination on January 10, 2011.

Vehicle toxicity was noted during dosing. Therefore, vehicles were changed several times during dosing to maintain the animal numbers. The final vehicle was established at week 26. The Sponsor performed a PK analysis to show that there was no loss of Cmax or AUC due to the vehicle changes.

From the Sponsor's Application: "From Day 1 through Week 13, the vehicle was 95% propylene glycol (PG)/5% ethanol (EtOH) (v/v) (pH 2.3 ± 0.1). Due to increased mortality in vehicle control animals compared to water control animals, the vehicle was modified slightly to 95% PG/5% EtOH (v/v) (not pH-adjusted) and was used from Weeks 14 through 25. At Week 26, due to continued higher mortality in the vehicle control mice, the vehicle was changed to 10% PG in 90% 40 mM acetate buffer (v/v) (pH 4.0 ± 0.1) which was used for the remainder of the study. Toxicokinetic data indicate that there were no notable differences in GS-9350 exposures associated with the change in vehicles."

Due to increased mortalities in both sexes, the high dose animals were sacrificed at week 95 (males) and week 88 (females). The remaining animals were sacrificed at week 97 (males) and 100 (females). Administration of GS-9350 did not have a negative impact on survival, and sufficient numbers of animals survived to adequately evaluate carcinogenicity.

Although there were significant modifications to the vehicle (due to survival issues), an adequate number of mice survived an appropriate duration (i.e., Weeks 97 or 100, males and females respectively, of the dosing phase) to result in acceptable exposure to the test article for a valid evaluation of the carcinogenic potential of GS-9350.

No significant increase in tumors was noted in either sex.

Executive CAC Recommendations and Conclusions:

Rats:

- The Committee agreed that the early deaths leading to premature study termination at weeks 97 (males) and 102 (females) did not preclude interpretation of the study.
- The Committee concurred that there was a drug-related increase in thyroid follicular cell adenomas (both sexes) and carcinomas (males only). This increase may be related to the hepatic enzyme induction.
- Labeling should include the increase in thyroid follicular cell adenomas (both sexes) and carcinomas (males only).

Mice:

- The Committee agreed that the early deaths leading to premature study termination at weeks 97 (males) and 100 (females) did not preclude interpretation of the study.
- The Committee concurred that there were no drug-related neoplasms in the mouse.

David Jacobson Kram, Ph.D., D.A.B.T
Chair, Executive CAC

cc:\

/Division File, DAVP, NDA 203-094

/Team leader, HGhantous, DAVP

/Reviewer, LMyers, DAVP

/PM, AOlagundoye,, DAVP

/DJacobson-Kram, OND IO

/AJacobs, OND IO

/PBrown, OND IO

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/s/

ADELE S SEIFRIED
03/27/2013

DAVID JACOBSON KRAM
03/27/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: March 15, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 51

Comments: Draft labeling revisions/proposals for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: March 15, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) - **Draft labeling revisions/proposals**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. Additional reference is made to DAVP draft labeling recommendations that were conveyed to you on March 12, 2013. Since then, the review team has made additional labeling revisions/proposals.

The following comments are being conveyed on behalf of the review team for your applications:

Please find the attached cobicistat label which contains the review team's suggested revisions, comments, and rationale. These labeling recommendations supersede the version that was sent to you March 12, 2013.

Please send your responses to the NDA by close of business on Thursday, March 21, 2013.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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ABIOLA M OLAGUNDOYE-ALAWODE
03/15/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: March 12, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 51

Comments: Draft labeling revisions/proposals for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: March 12, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) - **Draft labeling revisions/proposals**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. The following comments are being conveyed on behalf of the review team for your applications:

Please find below (and the attached cobicistat label) the review team's suggested revisions, comments, and rationale.

1. Further discussions were held internally by the FDA regarding the appropriateness of approving the proposed indication (b) (4)



2. For the GS-US-216-101 trial, please provide information on the following for cobicistat:
 - a. the storage temperatures at all storage sites (the trial site, any intermediate storage facilities, and the bioanalytical lab), and
 - b. the duration of storage at each site.

Please also comment on whether the existing cobicistat long term stability data covers the temperature and duration of cobicistat subject sample storage at each site.

3. For the GS-US-216-110 trial, in order to determine if the available long term stability data for cobicistat is applicable, please provide information on the anticoagulant that was used to collect cobicistat samples from this trial.

Please send your responses to the NDA by close of business on Thursday, March 21, 2013.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
03/12/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: February 26, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 4

Subject: - NDA 203094 Advice/Information request

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: February 26, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Clinical Advice/Information request

Please refer your New Drug Application (NDA) 203094 submitted June 26, 2012 for cobicistat tablets.

The following comments are being conveyed on behalf of the review team:

Because of potential confusion regarding the interchangeability of cobicistat and ritonavir, FDA has a communication plan timed to coincide with the cobicistat action. The primary message is that cobicistat is not directly interchangeable with ritonavir, with an emphasis on drug interactions. In addition to communicating the action and corresponding labeling and key messages via the HIV/AIDS listserv, we are planning a broader email "blast," stakeholder call, press release, and possibly a Medscape interview.

We also consider a Dear Healthcare Provider (DHCP) letter, targeted toward HIV providers and pharmacists, a key part of this plan. As such, the Division requests you prepare a DHCP letter in anticipation of the action date. The DHCP letter should highlight important information related to the safe and proper use of your product as described in the approved labeling, including but not limited to information contained in Indications and Usage (1), Dosage and Administration (2), and Warnings and Precautions (5). In particular, the DHCP letter should alert prescribers that the drug interaction profile of cobicistat differs from that of ritonavir and that caution should be employed when administering cobicistat with other concomitant medications.

Please submit a draft version of the DHCP letter to your NDA for Division review by March 8, 2013.

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Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
02/26/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: February 20, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 4

Comments: NDA 203094/0 Cobicistat- Clinical Pharmacology Information Request

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: February 20, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 Cobicistat- **Clinical Pharmacology Information Request**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. Also refer to your October 5, 2012 submission which contained your responses to DAVP information requests.

The following comment is being conveyed on behalf of the Clinical Pharmacology reviewer:

- In the GS-US-216-0110 trial, please clarify whether the atazanavir and ritonavir formulations are the U.S. commercially marketed formulations, the 100 mg cobicistat formulation is the Phase 1 formulation, and which of the three cobicistat formulations was used for the 150 mg dosing (in the eCTD submission for NDA 203094 please see Table 1 and Table 2 in 2.3.P.2-Pharmaceutical Development for information regarding the 100 mg and 150 mg cobicistat tablet strengths, respectively).

Please submit your response(s) to our request no later than Monday, February 25, 2013.

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Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Abiola M. Olagundoye-Alawode, PharmD
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Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
02/20/2013



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: February 8, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 51

Comments: Draft labeling revisions/proposals for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: February 8, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) - **Draft labeling revisions/proposals**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat.
The following comments are being conveyed on behalf of the review team for your applications:

Please find below (and the attached cobicistat label) the review team's suggested revisions, comments, and rationale.

Section 2.1 Recommended Dosage

We extended Table 1 to include patient populations based on labeling recommendations for use of the respective coadministered agent.

Section (b) (4) Renal Impairment

We moved the information regarding use of COBI with TDF to the Warnings and Precautions section (b) (4), where we created a separate subsection specifically for use with TDF.

Section (b) (4) Worsening Renal Impairment

We expanded this section to include general information regarding the effects of COBI on eGFR and specific information regarding use of COBI with TDF, including clinical cases of proximal renal tubulopathy (similar to STRIBILD labeling).

(b) (4)

We renamed this section and revised the text to caution prescribers that use of COBI with concomitant meds may result in drug interactions that cannot be predicted by RTV drug interactions.

Section 6.1 Clinical Trials Experience

We pooled Studies 105 and 114 throughout this section and updated the tables accordingly. We removed [REDACTED] (b) (4); instead, we added text summarizing the observed serum lipid changes.

- Please add the percentage of subjects taking lipid lowering agents at baseline per treatment group and the percentage of subjects that initiated lipid lowering agents while on treatment per treatment group to this section.

Section 7 Drug Interactions

In general, where applicable, only medications that have specific information regarding drug transporter interactions, routes of CYP metabolism or the potential for CYP inhibition or induction effects from the U.S. prescribing information are listed in Table [REDACTED] (b) (4). The metabolism and drug interaction information (including CYP enzyme and transporter interactions) from the U.S. prescribing information for atazanavir, darunavir, [REDACTED] (b) (4), ritonavir, cobicistat and the concomitant medications listed in Table [REDACTED] (b) (4) were reviewed. Subsequently, the appropriateness of extrapolating the predicted or observed interaction from the atazanavir, darunavir, [REDACTED] (b) (4) or ritonavir U.S. prescribing information to cobicistat coadministered with atazanavir, darunavir [REDACTED] (b) (4) was determined and the clinical comments were revised accordingly, if necessary.

Section 8.6 Renal Impairment

Section 8.7 Hepatic Impairment

When evaluating the effect of intrinsic factors, because atazanavir and darunavir exposures are similar when boosted with cobicistat or ritonavir, we simplified these sections by referring prescribers to the U.S. prescribing information for the respective coadministered medications.

[REDACTED] (b) (4)

Additional comment:

[REDACTED] (b) (4)

Please send your responses to the NDA by 12pm on Friday, February 22, 2013.

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Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
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Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
02/08/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: January 10, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 4

Comments: Pharmacology/Toxicology Information requests for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: January 10, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 (Cobicistat) - **Pharmacology/Toxicology Information Requests**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. The following comments/information requests are being conveyed on behalf of the Pharmacology/Toxicology reviewer:

Pharmacology/Toxicology

- 1, Concerning the 104 week oral gavage carcinogenicity study with GS-9350 (cobicistat) in mice, it is unclear whether the toxicokinetics (TK) of the drug were affected by the change in vehicles. The report states that the drug TK was not affected. Explain what data were used to support this hypothesis.
2. Please explain which exposure values were used for the calculation of the exposure margins listed on the draft label.

Please submit your response(s) to our requests no later than Tuesday, January 22, 2013.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
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Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
01/10/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: January 4, 2013

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 5

Subject: - Comments regarding your December 4, 2012 submission that contained response to
Clinpharm information request; Clinical information request

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: January 4, 2013

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: - Comments regarding your December 4, 2012 submission that contained response to Clinpharm information request
- Clinical information request

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat and to your December 4, 2012 submission.

The following comments are being conveyed on behalf of the clinical and clinical pharmacology reviewers:

Clinical Pharmacology

1. For the GS-US-216-130 trial, please clarify whether blood samples for cobicistat and darunavir were both drawn in K₂EDTA anticoagulated tubes.
2. For the GS-US-216-130 trial, please clarify the following:
 - a. For cobicistat and darunavir, please specify the sample storage conditions and the duration of storage (e.g. number of days) at the following locations:
 - i. trial sites (*please specify the maximum overall duration of storage at the trial sites*)
 - ii. (b) (4)
 - iii. the bioanalytical laboratory, for the period from the day samples were first drawn until the day the last sample was analyzed, including any reanalysis.
 - b. Based on the responses to comment 2a, please specify whether the established long-term stability data covers the necessary duration of storage and sample storage conditions for cobicistat and darunavir in K₂EDTA anticoagulated plasma.

3. For the long-term stability experiments that were conducted for darunavir and cobicistat, please confirm that the reference standards were used prior to the expiration dates and provide links to the relevant certificates of analyses.
4. Please submit the PBRL-RD-1371 method validation report (partial darunavir method validation) that was used for the analysis of darunavir samples from the GS-US-216-130 trial, including the available darunavir long term stability data at -20°C and -70°C in K₂EDTA anticoagulated plasma. Please also provide an updated version of the PBRL-RD-1041 method validation report (full darunavir method validation) that should include Amendment 1 to Addendum 3.
5. Please clarify whether the darunavir 400 mg tablets that were administered in the GS-US-216-130 trial, as well as the NRTIs (e.g. tenofovir, emtricitabine), are the U.S. commercially-marketed formulation.

Clinical

1. Please provide any and all information regarding the eight cases of nephrolithiasis reported in COBI-treated subjects in Studies -0105 and -0114, as well as the two cases of gallstones in Study -0114. Include any available case report forms, case narratives and results of laboratory test performed for each case (particularly if the stones were sent for biochemical analysis). Also provide a background summary of the incidence of kidney stones and gallstones observed in the COBI and STRIBILD development programs and a risk-benefit assessment for these safety issues.

The USUBJID numbers for the nephrolithiasis cases are:

GS-US-216-0105-0364-5510
GS-US-216-0105-0433-5565
GS-US-216-0105-1236-5515
GS-US-216-0114-0698-8166
GS-US-216-0114-0986-8244
GS-US-216-0114-0986-8283
GS-US-216-0114-0986-8458
GS-US-216-0114-1965-8024

The USUBJID numbers for gallstone cases are:

GS-US-216-0114-0684-8210
GS-US-216-0114-2856-8474

Please send your response(s) to your NDA on or before Monday, January 21, 2013.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
01/04/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: December 12, 2012

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 4

Comments: CMC Information request for NDA 203094

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: December 12, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 Cobicistat **CMC Information Request**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. Also refer to your November 27, 2012 submission which contained your responses to DAVP information requests.

The following comment is being conveyed on behalf of the Chemistry Manufacturing and Control (CMC) reviewer:

(b) (4)

(b) (4)

3. Please note that the expiration dating period begins when drug substance is first introduced into the drug product process. Therefore, please confirm the holding times for all of the (b) (4) intermediates (b) (4) are calculated into your drug product shelf-life.
4. We acknowledge your commitment to include microbiological purity testing in the stability protocol for the first three commercial batches of Cobicistat tablets. Provide the results of this testing in the NDA annual reports, along with your assessment of whether the results continue to support this approach to monitoring of microbial purity.

Please submit your response(s) to our request no later than noon, Friday, December 21, 2012.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
12/12/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: November 9, 2012

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 5

Comments: CMC/Biopharmaceutics Information request for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: November 9, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 Cobicistat **CMC/Biopharmaceutics Information Request**

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat.

The following comment is being conveyed on behalf of the Chemistry Manufacturing and Control (CMC) and Biopharmaceutics reviewer:

1. In regards to the DP manufacturing processes, we have the following recommendations:
 - a. In your most recent response to question #2 of the FDA's CMC Information Request dated September 6, 2012 (Reference ID: 3185550), you indicated that because of a delay in the validation plans a final commercial Master Batch Record (MBR) will not be available in the foreseeable future. Based on 21 CFR 314.50(d)(1)(ii)(c) we recommend that you provide at this time the current version of the commercial MBR, and/or a detailed manufacturing process description based upon the current version of the commercial MBR.

(b) (4)



(b) (4)

2. There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed design space would result in products that are bioequivalent. Submit adequate justification, including (but not limited to) the following information:
 - i. f2 statistical testing for COBI dissolution profile comparisons of tablets manufactured  (b) (4)  (Figures 4-5 in 3.2.P.2.3).
 - ii. Dissolution profiles and f2 statistical testing for COBI dissolution profile comparisons of tablets manufactured across the proposed ranges (provide the comparisons using a clinical batch as reference):
 (b) (4)
3. Replace Table 9 of 3.2.P.5.6 with updated information in Table 2 of 3.2.S.4.5 in DMF 25188. Revise the text of 3.2.P.5.6 accordingly.
4. Include microbiological purity testing for the cobicistat (COBI) tablets in the stability protocol for both the first three commercial batches and annual commitment batches at initial time point and at shelf life.
5. Include reporting of t =0 in the stability protocols for the first three commercial batches and annual commitment batches. Please update Tables 1 and 2 in section P.8.2, accordingly.

6. Submit a sample of COBI tablets, 150 mg, packaged in the proposed packaging configuration.
7. As a reminder of agreements reached under DMF 25188, measure (b) (4) level in the first five commercial batches from each DS manufacturing site.

Please submit your response(s) to our request no later than COB Tuesday, November 27, 2012.

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Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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ABIOLA M OLAGUNDOYE-ALAWODE
11/09/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: October 10, 2012

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 3

Comments: Information request for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: October 10, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 Cobicistat

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat and to your October 2, 2012 submission.

The following comment is being conveyed on behalf of the clinical pharmacology reviewer:

In addition to providing pharmacokinetic analyses and summary information in the Clinical Study Report, you should also provide pharmacokinetic data sets for darunavir and cobicistat from GS-US-216-0130 as SAS transport files (*.xpt).

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Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
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ABIOLA M OLAGUNDOYE-ALAWODE
10/10/2012



NDA 203094

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Beraud:

Please refer to your New Drug Application (NDA) dated June 27, 2012, received June 28, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cobicistat Tablets, 150 mg.

We also refer to your June 28, 2012 correspondence, received June 28, 2012, requesting review of your proposed proprietary name, Tybost. We have completed our review of the proposed proprietary name, Tybost and have concluded that it is acceptable.

The proposed proprietary name, Tybost, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if any of the proposed product characteristics as stated in your June 28, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Abiola Olagundoye at 301-796-3982.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
09/21/2012

CAROL A HOLQUIST
09/21/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 19, 2012

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Abiola Olagundoye-Alawode, Pharm.D. LCDR, USPHS Regulatory Project Manager
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 3

Comments: Information request for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 19, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 Cobicistat

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. The following comments are being conveyed on behalf of the clinical pharmacology reviewer:

1. In your responses received on August 21, 2012, you state that the GS-US-216-0130 trial evaluates the proposed U.S. to-be-marketed cobicistat formulation. Additional darunavir exposure data when coadministered with cobicistat as an 800 mg/150 mg once daily dosage regimen would be highly informative in comparing darunavir exposures for darunavir boosted with cobicistat compared to darunavir boosted with ritonavir. In addition, this data will assist in assessing the impact of any darunavir exposure differences on efficacy and safety. Please comment on the availability and feasibility of submitting the darunavir and cobicistat intensive and sparse PK data from the GS-US-216-0130 trial to the cobicistat NDA under review.
2. If the PK data from the GS-US-216-0130 trial are available and can be feasibly submitted, please provide a timeline for their submission.
3. If the above PK data are available and can be feasibly submitted, please clarify if the method validation and bioanalytical reports relevant to the analysis of darunavir and cobicistat plasma samples from the GS-US-216-0130 trial would also be available for submission.

Please submit your response to our request no later than October 2, 2012.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
09/19/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 29, 2012
TIME: 3:00 PM – 4:00 PM
LOCATION: Teleconference
APPLICATION: NDA 203094
DRUG NAME: Tybost (COBI)
TYPE OF MEETING: Teleconference

MEETING CHAIR: Peter Miele, M.D., Medical Reviewer

MEETING RECORDER: Abiola Olagundoye-Alawode, Pharm.D., RPM

FDA ATTENDEES:

Peter Miele, M.D., Medical Reviewer, Division of Antiviral Products (DAVP)
Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
Linda Lewis, M.D., Medical Team Leader, DAVP
Yanming Yin, Ph.D., Biometrics Reviewer, DAVP
Fraser Smith, Ph.D., Biometrics Reviewer, DAVP
Abiola Olagundoye-Alawode, Pharm.D., Regulatory Project Manager, DAVP
Karen Winestock, CPMS, DAVP

GILEAD SCIENCES ATTENDEES:

Andrew Cheng, MD, PhD, Senior Vice President, Clinical Research and Development
Operations
Paul Tomkins, PhD, Senior Director, Regulatory Affairs
Javier Szwarcberg, MD, MPH, Senior Director, Clinical Research and Project Team Leader
Michael Wulfsohn, MD, PhD, Vice President, Biometrics
Erika Liu, MS, Senior Director Stats Programming
Jay Huang, BSc, Manager, Stats Programming
Lijie Zhong, PhD, Director, Biometrics
Naomi Kautz, MSc, Senior Manager, Regulatory Affairs

BACKGROUND:

On June 27, 2012, Gilead Sciences, Inc. submitted new NDA 203094 for cobicistat.

The Division of Antiviral Products (DAVP) informed Gilead Sciences via electronic mail correspondence that the analysis datasets submitted for clinical studies GS-US-216-0114, -0105 and for the Integrated Summary of Safety are inconsistent with respect to the formatting used for reported dates. Some date variables appear to use a SAS code. Since this formatting issue is noted within and across multiple datasets, please resubmit the datasets using a consistent standard date format. In every dataset, all dates must be formatted as ISO date format.

TELECONFERENCE DISCUSSION POINTS:

Gilead agreed to provide the analysis datasets with the following additional information to facilitate FDA/DAVP review of the datasets:

1. Provision of a character ISO format date variable for all dates where there is only a numeric date variable
2. Formatting all numeric dates to be DATE9. format
3. The addition of treatment and demographic variables to the front of all analysis datasets (including start and end dates for treatment)

Additionally, the submission would contain brief clarifying points on the SAP-defined derivation of the treatment-emergent flag for AEs.

DECISIONS (AGREEMENTS) REACHED:

DAVP agreed with Gilead's plan to submit the revised data sets by September 6, 2012.

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
09/19/2012



NDA 203094

FILING COMMUNICATION

Gilead Sciences, Inc.
Attention: Naomi Kautz, MSc
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Kautz:

Please refer to your New Drug Application (NDA) dated June 26, 2012, received June 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for cobicistat 150 mg tablet.

We also refer to your amendments dated June 28, 2012, July 9, 2012, July 23, 2012, and August 21, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 28, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 31, 2013.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information no later than October 5, 2012:

Chemistry, Manufacturing and Control

1. The information about specifications for the starting materials which are presented in Module 2 should either be revised to incorporate recent revisions under Drug Master File (DMF) 25188, or replaced with a reference to that DMF.
2. Either revise the Description of the Manufacturing Process in 3.2.P.3.3 to make it comparably detailed to a batch record, or submit an unexecuted master batch record for the commercial drug product process.
3. Because cobicistat tablets may be used in all climatic zones world-wide, revise all post-approval stability protocols (b) (4) [REDACTED]
[REDACTED] Tables and text in sections 3.2.P.8.3 and 2.3.P.8 should be revised.
4. We note that you have presented Proven Acceptable Ranges (PAR) for process parameters in section P2.3 that were determined on the basis of multivariate studies. However, your section P3.3 includes only Normal Operating Ranges (NOR) or set points for the parameters, where the NOR are a subset of the PAR. Clarify, if you intend to handle movements within the PAR consistent with ICH Q8 (R2).

Clinical Pharmacology

Bioanalytical comments

5. In 2.7.1 (Summary of Biopharmaceutic Studies), in section 4.5, a summary of long term stability information for individual trials is provided. However, it is not clear whether all the storage conditions for the entire life cycle of a subject sample are included under "Transpired Time." For example, for desipramine, the storage conditions listed state that subject samples were stored for 49 days at -20°C. However, samples were actually stored at -70°C for approximately one month at the trial site and at -20°C for approximately one month at the bioanalytical laboratory.
 - a. Please update the table in section 4.5 to specifically include sample storage conditions and the duration of storage (e.g. number of days) at the following locations: 1) trial site, 2) any intermediate storage facility (if applicable), and 3) the bioanalytical laboratory from the day samples were first drawn until the day the last sample was analyzed, including any reanalysis.
 - b. If long term sample stability experiments were conducted in a different anticoagulant than samples were drawn in (e.g. digoxin samples from GS-US-216-112), please provide a rationale for extrapolating stability as a footnote to the table.

- c. For the analyses listed below, please submit the long term stability data that covers the sample storage conditions and the duration of storage at the three locations specified in 5a. Please also specify whether the reference standards for the long term stability experiments were used prior to the expiration date(s) and submit the relevant certificates of analyses with the long term stability data.
 - i. GS-US-216-112: efavirenz
 - ii. GS-US-216-123: rosuvastatin (at -20°C and -70°C) and rifabutin and 25-0-desacetyl rifabutin at -70°C.
 - iii. GS-US-216-105, GS-US-216-110, and GS-US-216-114: atazanavir and ritonavir at -20°C and -70°C.
6. Please submit or provide a cross reference for the following information that was submitted recently for NDA 203100 (including the relevant certificates of analyses):
 - the pending desipramine long term stability data at -70°C
 -
 - the (b) (4) 42-0930 method validation report for digoxin that contains long term stability data for digoxin in lithium heparin
7. For the cobicistat method (8212-867), please submit the freeze thaw stability data that support the storage and processing of cobicistat at -70°C for the GS-US-216-115 and GS-US-216-105 trials.
8. For both rosuvastatin and rifabutin, please submit the stock solution stability data at -20 °C (rosuvastatin), 4 °C (rifabutin) and at room temperature (both rosuvastatin and rifabutin) that are indicated as pending experiments in the method validation reports that were submitted.
9. For the (b) (4) 60-0949 cobicistat method validation, multiple QCs at 200 ng/mL reported %REs greater than 15% for the 124 hour post preparative stability at 4°C. For the GS-US-216-114, GS-US-216-116, GS-US-216-119, GS-US-216-121 trials that analyzed cobicistat samples using this method, please clarify if any cobicistat samples were stored at 4°C prior to initial analysis or were reinjected.
10. Please confirm that the blood samples collected for the following analyses were collected using the following anticoagulants that the methods were validated with:
 - a. cobicistat (GS-US-216-115): K₂EDTA
 - b. cobicistat (GS-US-216-105): K₂EDTA

11. For the cobicistat method ((b) (4) 60-0949) that references cobicistat long term sample stability data from (b) (4) please clarify if the same cobicistat analytical method was used by both laboratories. If different analytical methods were used, please provide a rationale for extrapolating long term stability to (b) (4) 60-0949.
12. For the cobicistat method ((b) (4) 8212-867), please clarify whether long term stability experiments were conducted for cobicistat and GS-9612. If long term stability experiments were not conducted, please specify the reference for the data that that supports the long term stability of cobicistat and GS-9612. If different analytical methods were used for the reference data and (b) (4) 8212-867, please provide a rationale for extrapolating long term stability to (b) (4) 8212-867.

Comments for clinical pharmacology trials

13.
 - a. For each of the trials below, please specify which of the three cobicistat formulations specified in Table 2 (2.3.P.2- Pharmaceutical Development) were administered:
 - i. GS-US-216-105
 - ii. GS-US-216-116
 - iii. GS-US-216-114
 - iv. GS-US-216-119
 - b. For the trials listed above, please confirm that the atazanavir, ritonavir, darunavir, or tenofovir and emtricitabine fixed dose combination (Truvada) drug products that were administered in the trials are the US marketed formulations.
14. Please submit either a cross reference to AD-216-2106 that was submitted to NDA 203100 or submit the in vitro report to NDA 203094.

Clinical

15.  (b) (4)

16. The analysis datasets submitted for clinical studies GS-US-216-0114, -0105 and for the Integrated Summary of Safety are inconsistent with respect to the formatting used for reported dates. Some date variables appear to use a SAS code. Since this formatting issue is noted within and across multiple analysis datasets, please resubmit the analysis datasets using a consistent standard date format. In every dataset, all dates must be formatted as ISO 8601 date format.

Biostatistics

17. Please identify the subjects who took other HIV drugs other than those drugs to which they were randomized. Subjects who received those HIV drugs after the date of their first dose and before their Week 48 visit should be treated as efficacy failures in the primary efficacy analysis according to the snapshot approach.

Please provide this information in a SAS dataset which should include: subject identification, the non-randomized HIV medication subject has taken, medication start and end dates, and Week 48 HIV RNA collection dates.

During our preliminary review of your submitted labeling, we have identified the following labeling issue and have the following recommendation:

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)

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. We request that you resubmit labeling that addresses this recommendation by Friday, October 5, 2012. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to: Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Abiola Olagundoye-Alawode, Pharm.D., Regulatory Project Manager, at (301) 796-3982.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
09/06/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 4, 2012

To: Naomi Kautz, M.Sc. Senior Manager, HIV Regulatory Affairs	From: Abiola Olagundoye, Pharm.D.
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796-9883
Phone number: 650-522-2789 Email: naomi.Kautz@gilead.com	Phone number: 301-796-3982

Total no. of pages including cover: 3

Comments: Information request for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: September 4, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information request for NDA 203094/0 (cobicistat)

Please refer to your New Drug Application (NDA) submitted June 26, 2012 for cobicistat.

The following comment is being conveyed on behalf of the biostatistics reviewer:

Please identify the subjects who took other HIV drugs other than those drugs to which they were randomized. Subjects who received those HIV drugs after the date of their first dose and before their Week 48 visit should be treated as efficacy failures in the primary efficacy analysis according to the snapshot approach.

Please provide this information in a SAS dataset which should include: subject identification, the non-randomized HIV medication subject has taken, medication start and end dates, and Week 48 HIV RNA collection dates.

Please send your response(s) to your NDA on or before Tuesday, September 11, 2012.

We are providing this above information via electronic mail for your convenience.

Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
09/04/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 4, 2012

To: Naomi Kautz, M.Sc. Senior Manager, HIV Regulatory Affairs	From: Abiola Olagundoye, Pharm.D.
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796-9883
Phone number: 650-522-2789 Email: naomi.Kautz@gilead.com	Phone number: 301-796-3982

Total no. of pages including cover: 4

Comments: Information request for NDA 203094

Document to be mailed: YES NO

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RECORD OF ELECTRONIC MAIL CORRESPONDENCE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: September 4, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: Information request for NDA 203094/0 (cobicistat)

Please refer to your New Drug Application (NDA) submitted June 26, 2012 for cobicistat and to your submission dated August 21, 2012 which contained your response to DAVP August 13, 2012 information request. The following comment is being conveyed on behalf of the biopharmaceutics reviewer:

In your response dated August 21, 2012, to the Information Request dated 13-AUG-2012, you state that (b) (4) Formulation 2) and the to-be marketed formulation are not significantly different in composition and in vitro performance (e.g dissolution profiles). However, upon comparison of the two formulations' composition, (b) (4) the formulations differ (b) (4) which according to current policy requires the submission of in vivo BA or BE information to support approval. (b) (4)

This information is relevant to understand whether your proposed dissolution method is capable of screening for differences in dissolution (if any) that may arise (b) (4)

Whether BA/BE information is needed to support this change in composition will be determined by the results of these additional dissolution data.

Please send your response(s) to your NDA on or before Monday, September 10, 2012.

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Please feel free to contact me at 301-796-3982 or 301-796-1500 if you have any questions regarding the contents of this transmission.

See electronic signature page

Abiola M. Olagundoye-Alawode, PharmD
LCDR, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
09/04/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 13, 2012

To: Naomi Kautz, M.Sc. Senior Manager HIV Regulatory Affairs	From: Karen Winestock Chief, Project Management Staff Division of Antiviral Products
Company: Gilead Sciences, Inc.	Division of Antiviral Products
Fax number: 650-522-5489	Fax number: 301-796- 9883
Phone number: 650-522-2789	Phone number: 301-796-0834

Total no. of pages including cover: 4

Comments: Information request for NDA 203094

Document to be mailed: YES NO

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FACSIMILE



**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: August 13, 2012

TO: Naomi Kautz, M.Sc.

SPONSOR: Gilead Sciences, Inc.

SUBJECT: NDA 203094/0 Cobicistat

Please refer your New Drug Application (NDA) submitted June 26, 2012 for cobicistat. The following comments are being conveyed on behalf of the clinical pharmacology reviewer:

1. For the GS-US-216-115 trial, it is noted in section 2.7.1 of the eCTD that cobicistat "Formulation 1" was administered. Please clarify if this formulation is the Phase 1/2 formulation (BB0902A) or the (b) (4) formulation (BB0904B) (b) (4) to produce the Phase 3/to-be-marketed formulation. Please also clarify if there is any bioavailability data linking (b) (4) (BB0904B) to the (b) (4) formulation actually administered in the Phase 3 trial (GS-US-216-0114).
2. If the Phase 1/2 formulation BB0902A was administered, please confirm that the GS-US-216-0116 trial is considered a pivotal BE trial linking the Phase 1/2 formulation (BB0902A) to the (b) (4) formulation (BB0904B).
3. Please provide supportive information for the statement in 2.3P.2 of the eCTD that the "Changes in the formulation composition had no effect on tablet performance" with respect to the (b) (4) formulation (BB0904B) that was (b) (4) to produce the Phase 3/to-be-marketed formulation.
4. For the GS-US-216-115 trial, please confirm that the darunavir and ritonavir "commercial products" administered in the 115 trial are the US marketed products.

Please submit your response to these issues no later than August 21, 2012.

We are providing this above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0834 if you have any questions regarding the contents of this transmission

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products

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/s/

KAREN D WINESTOCK
08/13/2012



NDA 203094

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Christophe Beraud, PhD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: cobicistat 150 mg Tablet

Date of Application: June 26, 2012

Date of Receipt: June 28, 2012

Our Reference Number: NDA 203094

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 27, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me at (301) 796-3982 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Abiola Olagundoye-Alawode, Pharm.D., RPh.
LCDR, USPHS
Regulatory Health Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
07/06/2012



IND 101283

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cobicistat.

We also refer to your December 22, 2011, correspondence, received December 23, 2011, requesting a meeting to discuss the results from the pivotal Phase 3 Study GS-US-216-0114 and to review the content and format of the NDA.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 30, 2012, 2:00 PM to 3:30 PM, EST between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Your questions are in bold font and the DAVP's preliminary responses are in italic.

Question 1

Gilead will be seeking an indication for cobicistat as a booster of HIV-1 protease inhibitors atazanavir (ATV) and darunavir (DRV). Refer to the Target Product Profile (Section 1 – Indication and Usage) provided in Attachment 3.

The proposed indication is based on the pivotal Phase 3 Study GS-US-216-0114 in treatment-naive adults showing non-inferiority of a COBI-boosted ATV (ATV/co)-based antiretroviral regimen to a ritonavir-boosted ATV (ATV/r)-based regimen, both in combination with Truvada (TVD), and on the comparative bioavailability (BA) Phase 1 Study GS-US-216-0115 in healthy adult volunteers showing the ability of COBI to boost the exposure of DRV similar to RTV. This indication will be further supported by 96-week safety and 48-week efficacy data from the Phase 2 Study GS-US-216-0105 of ATV/co vs. ATV/r, both in combination with TVD in treatment-naive adults. Furthermore, the Phase 2 and 3 studies with the EVG/COBI/FTC/TDF single-tablet regimen in treatment-naive, HIV-1 infected adults will provide additional safety data regarding COBI (b) (4)

Gilead anticipates submitting the NDA for COBI in Q2 2012.

A summary of the 48-week safety and efficacy data from the pivotal Phase 3 Study GS-US-216-0114 in support of the proposed indication for COBI as a booster of ATV is provided in Attachment 4. The Clinical Study Report for Study GS-US-216-0115 with PK data in support of the proposed indication of COBI as a booster of DRV was previously submitted to IND 101,283 (Serial No. 0083, 06 May 2010). In addition, PK/PD exploratory analyses of darunavir/ritonavir (DRV/RTV) supporting the use of COBI 150 mg-boosted DRV 800 mg once-daily dosing will be included in the NDA in accordance with the proposed indication.

A tabular presentation of the studies to be included in the application in support of the proposed indication for COBI tablets is provided in Table 1 below. Also refer to the approach for the presentation of the safety and efficacy data in the labeling as shown in the Target Product Profile (Section 14 – Clinical Studies and Section 6 – Adverse Reactions; Attachment 3).

Does the Agency agree that the proposed indication for COBI tablets is adequately supported by the pivotal and supportive studies listed in Table 1 and with the proposed approach to presentation of the safety and efficacy data in the labeling?

DAVP's Preliminary Response:

In general, the proposed indication appears reasonable; final wording will be contingent upon review of the data. Pivotal Study GS-US-216-0114, the comparative bioavailability Study GS-US-216-0115, and the supportive Study GS-US-216-0105 appear sufficient to support submission of an NDA for COBI tablets. It is unclear if data from Studies GS-US-236-0102, -0103 and -0104 will be helpful or necessary to support approval of COBI. As such, it is not necessary for you to resubmit all the study data to the COBI NDA. Instead, please provide a cross reference to relevant information from NDA 203100 in the COBI NDA. The proposed approach to presentation of the safety and efficacy data in the label appear reasonable; final wording will be addressed during the review process.

Question 2

A Target Product Profile for COBI tablets is provided in Attachment 3. Included in the Target Product Profile is a draft of the proposed drug interaction-related sections of the product label, together with the rationale and list of studies supporting the proposed text, as shown in Table 2 below.

Table 2. List of Drug Interaction-related Sections of the COBI TPP

Location	Section for Review
Section 5 – Warnings and Precautions	Section 5.1 Drug-drug Interactions Section 5.2 Use with Antiretrovirals
Section 7 – Drug Interactions	All of Section 7
Section 12 – Clinical Pharmacology	Section 12.3 – Pharmacokinetics, Assessment of Drug Interactions

Does the Agency have any comments regarding the proposed draft of the drug interaction-related sections of the COBI label as shown in the Target Product Profile?

DAVP's Preliminary Response:

Clinical

We consider information that the COBI tablet is not interchangeable with ritonavir as a pharmacokinetic enhancer to boost any HIV-1 protease inhibitors other than atazanavir or darunavir to be important information and should be made prominent in the label. In addition, the label should be explicit about not using COBI with saquinavir, fosamprenavir, tipranavir, lopinavir/ritonavir, or twice-daily darunavir.

Clinical Pharmacology

The Agency does not have any comments regarding the proposed formatting for the sections of the proposed cobicistat label related to drug-drug interactions.

Question 3

In consideration of the 48-week safety data from Study GS-US-216-0114, Gilead is not proposing a formal REMS strategy for COBI. Gilead plans, however, to insert cautionary text addressing drug-drug interaction potential in the COBI label (see relevant drug interaction-related sections included in Table 2).

Does the Agency consider this approach sufficient for risk mitigation of COBI?

DAVP's Preliminary Response:

Although a detailed examination of the COBI Target Product Profile has not been conducted, the general approach taken with respect to drug-drug interaction potential in the COBI label appears to be acceptable. While a formal REMS strategy is not foreseen at this time, please provide a description of your proposed education plan for COBI tablets in the NDA.

Question 4

Gilead plans to conduct integrated analyses of efficacy and safety from pooled data from the Phase 2 and 3 studies of ATV/co vs. ATV/r, both in combination with TVD, in HIV-1 infected, treatment-naive subjects (Studies GS-US-216-0105 and GS-US-216-0114) due to the similar design of these studies. These integrated analyses will be summarized in the Summary of Clinical Efficacy (m2.7.3) and the Summary of Clinical Safety (m2.7.4), with statistical outputs and electronic datasets provided in m5.3.5.3. For detailed descriptions of the integrated analyses of efficacy and safety from pooled data from the Phase 2 and 3 Studies GS-US-216-0105 and GS-US-216-0114, please refer to the Statistical Analysis Plans for the Integrated Summary of Efficacy (ISE) (Attachment 5) and the Integrated Summary of Safety (ISS) (Attachment 6).

In addition, an integrated analysis of the Phase 2 and 3 studies with EVG/COBI/FTC/TDF STR will be included within the Summary of Clinical Safety (m2.7.4), with statistical outputs and electronic datasets provided in m5.3.5.3. This integrated analysis of safety is the same as that submitted in the EVG/COBI/FTC/TDF STR Original NDA 203-100, Sequence 0000.

Does the Agency agree with the proposed approach for provision of the integrated analyses of efficacy and safety in the COBI NDA?*DAVP's Preliminary Response:*

The proposed approach for provision of the integrated analysis of safety in the COBI NDA appears reasonable. Please do not resubmit an integrated analysis of the Phase 2 and 3 studies with the EVG/COBI/FTC/TDF tablet within the Summary of Clinical Safety (m2.7.4), with statistical outputs and electronic datasets provided in m5.3.5.3 in the COBI NDA. Rather, please provide a cross-reference to these data in NDA 203100.

Question 5

As part of the EVG/COBI/FTC/TDF STR NDA 203-100 Safety Update, Gilead submitted updated safety information (deaths, SAEs, discontinuations due to AEs, AEs of interest) for a number of ongoing COBI, EVG and EVG/COBI/FTC/TDF STR studies. In order to supplement the body of data existing in the clinical study reports included in the COBI NDA, Gilead plans to include the data from the NDA 203-100 Safety Update in the COBI NDA as shown in Table 3 below. A copy of the EVG/COBI/FTC/TDF STR Safety Update together with statistical outputs will be provided in Module 5.3.5.3.

Does the Agency agree with Gilead's plan to include data from the EVG/COBI/FTC/TDF STR NDA 203-100 Safety Update in the NDA for COBI tablets?

DAVP's Preliminary Response:

We agree with the proposal to include information from the NDA 203100 Safety Update in the COBI NDA. However, please do not resubmit data from the EVG/COBI/FTC/TDF tablet studies to the COBI tablet NDA. Rather, please provide a cross-reference to these data in NDA 203100. We note that the COBI NDA Safety Update will also include updated safety information for ongoing trials with the EVG/COBI/FTC/TDF tablet through mid-May 2012.

Question 6

The draft Table of Contents for the COBI NDA is provided in Attachment 7. Please note that the list of bioanalytical and analytical methods and validation reports are not included in m5.3.1.4 and m4.2.2.1 of this draft Table of Contents but will be included in the COBI NDA submission.

Does the Agency have any comments regarding the list of nonclinical and clinical studies to be included in the COBI NDA?DAVP's Preliminary Response:

The proposed list of clinical studies to be included in the COBI NDA is acceptable.

Please do not resubmit all nonclinical study reports listed in module 4 that were submitted to NDA 203100, but rather only include new information that has not been previously submitted. Please provide a cross-reference to these data in NDA 203100.

Question 7

Gilead plans to follow the approach agreed upon with the Agency and used for NDA 203-100 for EVG/COBI/FTC/TDF STR as shown in Table 4 below.

Table 4. Proposals for COBI Tablets NDA Structure and Content

Modules	Structure/Format Description	Supporting Correspondence
m2.7.2; m5.3.5.4	Nonclinical and clinical virology study reports will be included in m5.3.5.4, and summarized in m2.7.2	EVG/COBI/FTC/TDF STR pre-NDA meeting comments, 08 July 2011
m2.6.2; m2.6.4	The primary pharmacodynamics (PD) of COBI is inhibition of CYP3A-mediated metabolism. Gilead will summarize the PD of the drug in m2.6.4, with a brief note in m2.6.2.	EVG/COBI/FTC/TDF STR pre-NDA meeting comments, 08 July 2011
m2.7.2; m5.3.4.1	Electronic datasets and electrocardiogram waveforms for the thorough QT/QTc study with COBI (Study GS-US-216-0107) were previously submitted to IND 101,283 and will not be included in the COBI NDA. The data from this study will be summarized in m2.7.2 and the study report included in m5.3.4.1.	EVG/COBI/FTC/TDF STR pre-NDA meeting comments, 08 July 2011

m5; CRFs	Case report forms (CRFs) will be provided for deaths, serious adverse events, discontinuations due to adverse events, and adverse events of interest for all randomized subjects.	EVG/COBI/FTC/TDF STR pre-NDA meeting comments, 08 July 2011
m5; Datasets	Electronic datasets for Phase 1, 2 and 3 studies will be provided in SAS XPORT transport format. Electronic datasets for GS-US-216-0114 and GS-US-216-0105 will be provided using CDISC SDTM version 1.2 (12 November 2008), CDISC SDTM IG version 3.1.2 (12 November 2008), and CDISC Analysis Data Model Version 2.1. CDISC ADaM IG version 1.0. HIV template datasets will also be provided for GS-US-216-0114 and GS-US-216-0105 (blinded phase only). Electronic analysis datasets for Phase 1 studies will not be provided using CDISC SDTM and ADaM format but rather using Gilead's internal analysis dataset format. Datasets for the integrated analysis of safety will be provided following CDISC Analysis Data Model Version 2.1 and CDISC ADaM IG version 1.0. Overall, the format of the datasets for the COBI NDA will be the same format as those provided for the EVG/COBI/FTC/TDF STR NDA.	FDA communication from EVG/COBI/FTC/TDF STR program, 14 Apr 2011, 01 June 2011, 29 June 2011

Does the Agency agree with the proposals detailed above for the content and structure of the application?

DAVP's Preliminary Response:

Please confirm that the CRFs for AEs of interest will include renal, bone, hepatic, and rash events. In addition, please include CRFs for subjects who discontinue due to "other" reasons.

Please show all changes from baseline in your resistance datasets, not just selected substitutions.

Question 8

Gilead proposes to include in the COBI NDA m1 documentation for investigator financial disclosure, source documents for treatment allocation codes, statement of availability of HIV-1 RNA and CD4 cell count, disclosure of financial agreement with vendors used to manage treatment allocation codes, and investigator contact information, as detailed in Table 5 below.

Table 5. List of m1 Documentation for Pivotal and Supportive COBI studies

Module 1 Section	Document Description	COBI NDA
1.3.4	Financial certification and disclosure	GS-US-216-0114 GS-US-216-0115 GS-US-216-0105

1.11.3	Gilead source documents for treatment allocation codes ^a	GS-US-216-0114 GS-US-216-0105
1.11.3	Vendor source documents for treatment allocation codes ^a	GS-US-216-0114 GS-US-216-0105
1.11.3	Statement of availability of HIV-1 RNA and CD4 cell count laboratory source documents at clinical sites ^b	GS-US-216-0114 GS-US-216-0105
1.11.3	Disclosure of Financial Agreements between Gilead and vendor(s) used to generate and manage treatment allocation codes ^a	GS-US-216-0114 GS-US-216-0105
1.11.3	Investigator contact information	GS-US-216-0114 GS-US-216-0115 GS-US-216-0105

a Does not apply to Study GS-US-216-0115, which is an open-label study

b Does not apply to Study GS-US-216-0115, which was conducted in healthy volunteers

Gilead does not intend to provide this information for the Phase 2 and 3 studies with EVG/COBI/FTC/TDF STR, as this information has already been submitted to NDA 203-100.

Does the Agency agree with the proposal for provision of the m1 documentation described in Table 5?

DAVP's Preliminary Response:

We concur with the proposal.

Question 9

Per 21CFR314.50(d)(5)(vi)(b) Gilead plans to submit a Safety Update 120 days following the submission of the COBI NDA for ongoing clinical studies listed in Table 6 below. The Safety Update will include cumulative deaths, serious adverse events, discontinuations due to adverse events, and adverse events of interest. The data cut-off dates for the Safety Update are provided in Table 6.

Does the Agency agree with the proposal for the scope of the COBI NDA Safety Update?

DAVP's Preliminary Response:

The proposal for the COBI NDA Safety update is acceptable.

Additional comments

Clinical Pharmacology

1. *In the Summary of Clinical Pharmacology Studies (2.7.2) for the NDA submission:*

- a. *For each of the drug-drug interactions listed in section 7.3, Table 5 that are based on extrapolation, please clarify how the drug-drug interaction data will be presented to justify the extrapolation, including providing references to the relevant drug-drug interaction data.*

- b. *In support of the statement in section 7.1 of the proposed label* (b) (4)

(b) (4)

- (b) (4) please provide a rationale (b) (4)
(b) (4) consistent with
g interaction studies.
- Please separate out the method validations report and the bioanalytical reports as stand alone submissions in the eCTD format rather than including them as attachments to the clinical study reports. The clinical pharmacology team recommends listing all method validation reports separately in section 5.3.1.4 and in section 5.3, each bioanalytical report should be listed as a separate document within the subfolder containing the report for the clinical trial.
 - As part of the bioanalytical information that is included in the Summary of Biopharmaceutic Studies (2.7.1), for each trial, please provide information on the duration samples were first drawn to the date of last sample analysis (including ISR) and the storage temperature for the samples at the trial site, intermediate storage facilities (if applicable), and the bioanalytical laboratory. Please state whether both the storage duration and the temperature throughout a sample's life cycle is supported by the long term stability data for each analyte.
 - In section 12.2 of the proposed cobicistat label, the information indicates that the pharmacokinetic enhancing effects of cobicistat versus ritonavir when coadministered with darunavir are comparable. However, it was noted in the GS-US-216-115 trial that the 90% confidence interval for the darunavir C_{tau} ratio with (b) (4) ing darunavir/cobicistat to darunavir/ritonavir was not within (b) (4). Please clarify whether additional information (e.g. exposure-response or (b) (4) ysis) will be included in the NDA to support the efficacy and safety of darunavir when coadministered with cobicistat, including evaluating the clinical significance of the differences in the C_{tau} (please also refer to the meeting minutes for the March 2010 cobicistat EOP2 meeting [Question 2b]).

BioPharmaceutics / Chemistry, Manufacturing and Control

- A dissolution method development report should be included in the NDA. The dissolution report generally contains the following information:

 - Solubility data for the drug substance covering the pH range
 - Detailed description of the dissolution method and the developmental parameters (equipment/apparatus selection, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions etc) used to select the most appropriate method. The testing conditions used for each test should be clearly specified
 - The complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time, and
 - Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as validation data for the dissolution method and analytical method

We have the following comments regarding the proposed pediatric program:

- While we do not consider switch studies optimal for assessing efficacy of a new ARV drug or regimen, this design is acceptable because the objective is to match exposure of the anchor drug and not COBI.
- In the setting of developing a PK enhancer, strong justification of the proposed boosting dose of COBI is critical because of the impact on the entire regimen's success or failure.
- While the adult program has succeeded in identifying a single dose of COBI for boosting all ARVs for which the PK booster indication is being sought, this may be more difficult in pediatric patients. Please describe your criteria for recommending dose adjustment.

In pediatric patients, exposures lower than the target values are less acceptable than exposures higher than the target because the impact of resistance is great in patients receiving a lifetime of ARV therapy. In addition, describe how you plan to adjust dosing of the PI and/or COBI if exposure at the initial selected dose does not match the approved pediatric dosing for that PI. If at all possible, dosing of the approved PI should not be adjusted.

- *At present, the only approved regimen of DRV in pediatric patients is twice daily administration. Additional justification and confirmatory safety data will be required to support a twice daily regimen of COBI.*
- *Once daily DRV is not approved for pediatric patients. Alternately, you could develop a pediatric program to directly evaluate once daily DRV/COBI.*
- *Please provide your plans for evaluating other PI/COBI combinations.*

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

IND 101283

Pre-NDA preliminary comments

Page 10

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

You should provide to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-3982 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Abiola Olagundoye-Alawode, Pharm.D., RPh.
Regulatory Health Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ABIOLA M OLAGUNDOYE-ALAWODE
03/27/2012



IND 101,283

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Christophe Beraud, Ph.D.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Beraud:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GS-9350.

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2010. The purpose of the Type B, End of Phase 2 meeting was to review the nonclinical, Phase 1 and Phase 2 clinical data and to provide comments on the design of the Phase 3 studies of GS-9350. We also discussed the key aspects of the development plan for GS-9350, including the data required to support an indication to boost antiretrovirals including (b) (4), atazanavir (ATV), and darunavir (DRV).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Stacey Min, Pharm.D., Regulatory Project Manager at (301) 796-4253.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 12, 2010

TIME: 1:00 – 2:30 PM

LOCATION: White Oak, CSU, E-2046

APPLICATION: IND 101,283

DRUG NAME: GS-9350

TYPE OF MEETING: Type B Meeting

MEETING RECORDER: Stacey Min, Pharm.D., Regulatory Project Manager

FDA ATTENDEES:

Debra Birnkrant, M.D.	Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., MPH	Deputy Director, DAVP
Linda Lewis, M.D.	Medical Team Leader, DAVP
Peter Miele, M.D.	Medical Officer, DAVP
Kellie Reynolds, Pharm.D.	Deputy Director, Division of Clinical Pharmacology 4 (OCP/DCP4)
Sarah Robertson, Pharm.D.	Clinical Pharmacology Team Leader, (OCP/DCP4)
Vikram Arya, Ph.D.	Clinical Pharmacology Reviewer, (OCP/DCP4)
Peyton Myers, Ph.D.	Pharmacology/Toxicology Acting Team Leader, DAVP
Greg Soon, Ph.D.	Biometrics Team Leader, DAVP
Wen Zeng, Ph.D.	Biometrics Reviewer, DAVP
Julian O'Rear, Ph.D.	Clinical Virology Team Leader, DAVP
Takashi Komatsu Ph.D.	Clinical Virology Reviewer, DAVP
Mark Seggel, Ph.D.	Product Quality Acting Team Leader, Office of New Drug Quality Assessment IV (ONDQA IV)

Kimberly Struble, Pharm.D.
Victoria Tyson
Vanessa Perry, M.S.
Camille Bossard
Stacey Min, Pharm.D.

Medical Team Leader, DAVP
Chief, Project Management Staff, DAVP
Regulatory Project Manager, DAVP
Student Intern
Regulatory Project Manager, DAVP

EXTERNAL CONSTITUENT ATTENDEES:

Gilead Sciences, Inc:

Roy Bannister, Ph.D., DABT
Christophe Beraud, Ph.D.
Brian Kearney, Pharm.D

Steven Chuck, M.D.
Paul Tomkins, Ph.D.

Director, Drug Safety Evaluation
Senior Manager, Regulatory Affairs
Senior Director, Clinical Research and
Clinical Pharmacology, Project Leader
Vice-President, Clinical Research
Senior Director, Regulatory Affairs

1. BACKGROUND

Gilead Sciences Inc. is developing a new chemical entity, GS-9350 under IND 101,283 as a pharmacoenhancer to increase the systemic levels of coadministered antiretroviral agents metabolized by CYP3A enzymes, including [REDACTED]^{(b) (4)} atazanavir (ATV) and darunavir (DRV).

Gilead has conducted Phase 1 and 2 studies to study the effects of GS-9350 as a pharmacoenhancer for once daily [REDACTED]^{(b) (4)} ATV, or DRV. GS-9350 is also under development as a fixed-dose combination (FDC) tablet consisting of EVG/FTC/TDF/GS-9350 under IND 103,093.

Gilead requested this Type B, End-of-Phase 2 meeting to discuss the nonclinical, Phase 1 and Phase 2 clinical data with GS-9350 and the FDC tablet and to seek agreement on key aspects of the development plan for GS-9350, including data required to support an indication to boost antiretrovirals including [REDACTED]^{(b) (4)} ATV and DRV.

2. DISCUSSION

Question 1

Does the Agency agree that Phase 3 clinical studies of GS-9350 as the stand-alone tablet or as part of the EVG/FTC/TDF/GS-9350 FDC tablet can proceed?

We agree that Phase 3 clinical studies of GS-9350 may proceed. See, however, comments below regarding GS-9350's boosting effect of darunavir and further protease inhibitor (PI) boosting studies.

Discussion: No further discussion.

Question 2a

Does the Agency have any comments regarding the Phase 3 study of GS-9350-boosted ATV versus RTV-boosted ATV both in combination with Truvada (FTC/TDF) in treatment-naïve, HIV-1 infected subjects (Study GS-US-216-0114), as the pivotal study to support the approval of GS-9350 as a booster of ATV?

- We agree with the trial design, study population and endpoints of GS-US-216-0114. The 12% of non-inferiority margin used for ART-naïve subjects is acceptable for planning purposes and study design but will be assessed further during the review.*

Discussion: No further discussion.

- *We note that you intend to use the TLOVR algorithm. The Division has recently switched to the snapshot methodology. A document containing recommendations on conducting the snapshot analysis will be made available to you in the near future. Please change the primary efficacy endpoint to the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. The TLOVR algorithm for HIV-1 RNA <50 copies/mL through Week 48 should be used for one of your secondary efficacy endpoints.*

Discussion:

The Agency informed Gilead that TLOVR method of analyses will no longer be used for the primary endpoint but has been replaced with the snapshot methodology. The snapshot analyses will be implemented for all studies moving forward. The Agency will finalize documents on conducting the snapshot analyses and will send recommendations to Gilead next week. Gilead asked the Agency about subjects who switch therapy. The Agency responded that if a new antiretroviral (ARV) is added to a subject's regimen, the subject will be classified as failure whether or not the viral load is greater than 50 copies/mL in the window. Switches for documented toxicity reasons are permitted on or before the first trial visit without penalty. If the switch occurs after the first trial visit, patients are considered failures if they have HIV-1 RNA > 50 copies/mL at time of the switch. The Agency asked Gilead to define acceptable therapeutic switches. The Agency agreed that the TLOVR analysis need not be a prespecified secondary endpoint, but acknowledged that having the TLOVR analysis would be useful as the Agency plans to compare both analyses. Gilead agreed to make the TLOVR secondary analyses available.

- *We also note that the control arms for GS-US-216-0114 and GS-US-236-0103 are identical, namely ritonavir-boosted atazanavir plus FTC/TDF. The Division suggests you consider combining the two studies into a single study with one comparator arm in order to conserve study subject populations.*

Discussion:

Gilead thanked the Agency for the suggestion, but indicated that it would be logistically difficult to combine the two trials into a single, 3-arm trial due to issues of blinding. Subjects would be required to take more pills and the duration of the trial would have to be extended. Gilead will conduct the two separate trials, GS-US-216-0114 and GS-US-236-0103, as originally planned. Gilead plans to start the trials soon and will incorporate the snapshot methodology in the statistical analysis plan (SAP). The Agency agreed.

Question 2b

Does the Agency agree that the proposed development plan will support the registration of GS-9350 tablet as a pharmacoenhancer of (b) (4) DRV?

The proposed development plan seems appropriate. Please be aware of the following:

- *When co-administered with GS-9350 (either once daily or twice daily), if PI exposures are determined to be lower than the PI exposures when co-administered with ritonavir (RTV) at the approved PI/RTV dose, supporting efficacy data will be needed. If PI/GS-9350 exposures are higher than PI/RTV exposures, then supporting safety data will be needed. If supporting efficacy or safety data cannot be provided to support the lower or higher PI exposures observed with GS-9350, additional evaluation in HIV-infected patients will be necessary to determine the clinical relevance of the increased or decreased pharmacokinetic (PK) parameters of the PI.*

Discussion:

Gilead agreed that strict bioequivalence of PI exposure when co-administered with RTV or GS-9350 is ideal and asked the Agency about the clinical data that would be required if strict bioequivalence is not demonstrated. In the case of DRV, Gilead noted that C_{tau} was not bioequivalent between RTV and GS-9350 boosting but C_0 was bioequivalent, and that C_0 is reflected in the DRV label. The Agency informed Gilead they have not seen the full study report for the PK study performed with DRV + GS-9350. Gilead indicated they would provide supporting data obtained from literature, the DRV label and from Tibotec to support the efficacy of DRV when boosted with GS-9350. The Agency asked if Gilead had any arrangement with Tibotec. Gilead indicated there was no formal arrangement, but that they have been in communication with Tibotec regarding the use of DRV with GS-9350. The Agency informed Gilead that a Right of Reference would be required to use any of the previously submitted DRV data in an NDA for GS-9350. The Agency stated that in the event the PK parameters are matched for a given PI boosted with GS-9350, the need for further clinical data in HIV patients will be evaluated on a case-by-case basis and will depend on the outcome of ongoing trials of atazanavir/GS-9350 and other PK data.

Question 3

Does the Agency agree with the possible staggered filing of the GS-9350 tablet NDA relative to the NDAs for EVG tablets and EVG/FTC/TDF/GS-9350 FDC tablet?

We agree with the possible staggered filing of the GS-9350 tablet NDA relative to the NDAs for EVG tablets and the FDC tablet. The content and format of the NDAs will require further discussion at the Pre-NDA meetings. Please be aware, if you submit the EVG and FDC tablet NDAs prior to the GS-9350 NDA, you will be eligible for three years of exclusivity, rather than five years of exclusivity, for a new chemical entity.

Discussion:

Gilead acknowledged that they will only be eligible for three years of exclusivity if the GS-9350 NDA is submitted after the NDAs for EVG and the FDC tablet. The Agency

inquired about the reason for the delay in filing the NDA for GS-9350 compared to the two other NDAs. Gilead stated that logistically it would be difficult to submit three NDAs simultaneously. Gilead will submit the product quality information for GS-9350 with the NDA for the FDC tablet.

Question 4a

Does the Agency agree that the proposed plan to study drug interactions between GS-9350 and other PIs, including those administered twice-daily is sufficient to support registration of GS-9350 and to provide appropriate drug interaction labeling information for these agents?

The proposed plan seems appropriate. Please address the following:

- *Will dosing recommendations pertaining to the concomitant use of all of the PIs (used once or twice daily) and GS-9350 be available at the time of submitting the registration application for GS-9350 as pharmacoenhancer for ATV and DRV?*

Discussion:

Gilead indicated that following an evaluation of GS-9350 with (b) (4) atazanavir (ATV) and DRV, (b) (4) will be evaluated. In addition, the feasibility of twice-daily dosing with GS-9350 will be addressed (b) (4). The Agency agreed that the proposal seems appropriate and expressed that determination of an appropriate dose may not be feasible or necessary for every PI. The need for additional studies with other PIs will be determined by the results of ongoing and planned PK studies. The Agency, however, encouraged Gilead to obtain as much data as possible for all of the approved PI regimens, such that an appropriate dose or recommendation for use can be clearly stated in the GS-9350 label for each PI in order to prevent off-label use. Gilead stated that a study to evaluate the PK and safety of GS-9350 twice daily and additional studies including GS-9350 plus twice daily DRV will be provided in the original NDA.

Question 4b

Does the Agency agree that the plan to evaluate the drug interaction potential of GS-9350 with key concomitant medications and to study GS-9350 in special populations is sufficient to support registration of GS-9350?

The need for additional drug-drug interaction studies (in addition to the studies outlined in the meeting package) will be determined by the results of ongoing and planned drug-drug interaction studies. For example, the results from the planned "cocktail" study will help determine the need for evaluating the drug-drug interaction potential of GS-9350 with other antiretroviral and non-antiretroviral drugs.

Please address the following:

- a) *How will drug-drug interaction information be extrapolated from a “PI/RTV/co-administered drug” combination to “PI/GS-9350/co-administered drug” combination?*

Discussion:

Gilead acknowledged that the cocktail study and planned drug interaction studies with oral contraceptives and opiate replacement therapy will provide additional information to help determine the need for additional drug interaction studies. Gilead stated that they intend to systematically address each of the established DDIs for a given PI and will determine the need for data with GS-9350 + the PI + coadministered drug on a case-by-case basis. The Agency stated that there are many factors and pathways involved in PI/RTV interactions with other drugs and a rationale will need to be provided for each combination.

- b) *Has GS-9350 been evaluated as a potential substrate, inducer, or inhibitor for transporters OATP1B1, OATP1B3 and BCRP? Since ritonavir is an inhibitor of OATP1B1 and OATP1B3, the extrapolation of certain drug-drug interactions for a particular PI/RTV combination will require knowledge of GS-9350 specificity for these transport proteins.*

Discussion:

Gilead stated that they have developed assays for these transporters and will be conducting these in vitro studies soon.

- c) *Given that the observed increase in serum creatinine with GS-9350 is being described as consistent with inhibition of active tubular secretion of creatinine, similar to that observed with cimetidine, please comment on plans to evaluate the specificity or inhibition potential of GS-9350 for OCT transporters.*

Discussion:

The Agency reviewed the draft Phase 3 protocol for GS-9350 and asked Gilead to consider lowering the screening CrCL criterion to > 50 mL/min in order to evaluate the effect of GS-9350 in subjects with renal impairment. Alternatively, Gilead could conduct additional studies in subjects who fail to meet the CrCL criterion for the Phase 3 trial. Gilead clarified that CrCL > 70 mL/min will remain the screening criterion for the Phase 3 trial. Given the observed renal toxicities with tenofovir, the Agency inquired how Gilead plans to monitor for early signs of renal toxicity during the course of the trial. Gilead will provide investigators with CrCL calculations and estimated creatinine clearance on a regular basis.

Gilead plans to conduct a renal impairment study of GS-9350 in healthy subjects to determine the effect on safety (SCr and GFR) and PK. The Agency informed Gilead that longer duration data in HIV-infected subjects is desired. This may be accomplished by lowering the screening CrCL criterion to 50 mL/min in the Phase 3 trial or conducting separate studies. The Agency asked Gilead to include data on subjects with renal impairment with the NDA submission. Otherwise, this issue may generate a postmarketing commitment (PMC).

Question 5

Does the Agency have any comments regarding the timing and scope of the proposed pediatric development plan?

A more detailed discussion of your pediatric development plan may be needed in the near future. We recommend that you provide a more detailed plan with draft protocols or synopses as soon as they are available and urge you to begin pediatric PK, safety and activity studies simultaneously with the adult Phase 3 studies unless you identify a safety issue of specific concern in pediatric patients. We also recommend you submit copies of any communications you have had with the EMA regarding pediatric drug development. In the absence of significant safety issues, it is not necessary to stagger studies of different pediatric age groups (i.e., adolescents, then school age children, then younger children and infants) as this tends to delay collection of important pediatric data.

DAVP plans to issue a Written Request (WR) for Pediatric Studies for both EVG and GS-9350. The WR for EVG will closely parallel those for other antiretroviral drugs (see example/template posted on FDA's Pediatric website). The WR for GS-9350 is likely to be similar in scope, but internal discussion may be needed to determine how much pediatric PK and safety data are needed across age groups for a new PK enhancer. In addition, under the Pediatric Research Equity Act, all submitted NDAs, including those for fixed-dose combination products, may be subject to post-marketing requirements to evaluate new products in pediatric patients if they are likely to provide a public health benefit. All NDAs must contain a pediatric assessment and requests for waivers or deferrals of pediatric studies must be justified at the time of NDA submission.

We also question the feasibility of switch studies as a means to evaluate GS-9350 in adolescents, as we have recent examples that this type of study may be prone to failure.

Discussion:

Gilead indicated plans to submit pediatric investigational plans to all three INDs by end of May, 2010. The Agency explained that it is very likely that a pediatric assessment deferral or waiver with justification will be required for any NDA submission, including the EVG stand-alone NDA. The Agency informed Gilead of recent feedback from the Pediatric Review Committee (PeRC) that tablets of particular size or fixed-dose formulations might not be granted a waiver for pediatric studies if the FDC tablet provides a public health benefit. Therefore, it is possible that pediatric studies may still be

required for the FDC tablet in younger patients. The Agency advised Gilead to consider developing a scored or smaller size tablet. Gilead has discussed internally the pediatric studies for the FDC tablet and stated it may be a challenge to develop a lower-dose FDC tablet if each of the four components needs to be adjusted differently. Gilead is also not sure if the weight bands for tenofovir dosing can be collapsed. The Agency referred to data for the tenofovir 75 mg tablet and PEPFAR products that are available for pediatric populations. The Agency stated pediatric studies will likely require further discussion.

The Agency inquired about Gilead's plans to use switch studies to evaluate GS-9350 in adolescents as the Agency's experience with switch studies has shown them to be prone to failure. Gilead plans to evaluate a switch from RTV to GS-9350 only. The Agency advised Gilead to consider other study designs because tolerability and adherence issues following a switch in one or more drugs can result in poorer outcomes.

Gilead asked if the Agency would permit extrapolation of safety and efficacy data from adult studies. The Agency responded that it is possible to extrapolate from adult data to pediatrics and the Agency acknowledges the difficulty of enrolling comparative studies in children due to the small number of subjects. Single-arm pediatric studies are often acceptable. The Agency will consider extrapolation of adult data but adequate safety data will be needed. The Agency informed Gilead that the primary outcomes for pediatric studies should be PK and safety, with efficacy extrapolated mainly from adult studies; virologic outcomes are evaluated as secondary endpoints. Gilead inquired whether 24 weeks of pediatric trial data will be suitable to demonstrate efficacy. The Agency noted that 24 weeks is a little short but will make a determination based on a review of the data.

Additional discussion:

The Agency reiterated the renal toxicity issue with GS-9350 and also inquired about the effect on PR prolongation and bilirubin levels. Gilead responded that they have not seen an effect on PR prolongation in Phase 2 studies with GS-9350. Increases in bilirubin increases were similar in the ATV/RTV and ATV/GS-9350 arms of the study. No increases in bilirubin, liver enzymes or PR prolongation were observed with the FDC tablet in Phase 2 trials.

In the thorough QTc study conducted with GS-9350, PR prolongation was observed in the supratherapeutic range. However this study is still under review by the Agency's IRT. The Agency re-emphasized a comment sent to Gilead regarding the EVG single-drug TQTc study which questioned whether the supratherapeutic dose was high enough. The Agency stated they would re-send the comment.

Question 6

Does the Agency have any comments on the completed and planned nonclinical toxicology package for GS-9350 and its adequacy to support registration?

The nonclinical package appears adequate.

Discussion: No further discussion.

Question 7

Does the Agency agree with our proposal for submission of study analysis datasets, CRFs, or laboratory data in the NDA for GS-9350, but also the associated NDAs for EVG/FTC/TDF/GS-9350 and EVG?

The proposal for submission of study analysis datasets is acceptable. Please submit the SAS programs for generating the analysis datasets and primary efficacy endpoint analyses. In addition to submission of these data, other efficacy datasets may be requested for the NDA submission. The specification of these other datasets will be provided at a later date and further discussion regarding dataset formats may be held at the pre-NDA meeting.

Discussion:

Gilead requested clarification on whether SDTM (Study Data Tabulation Model) data format will become mandatory. The Agency stated that SDTM data format is recommended but not mandatory but asked Gilead to submit the data in this format as it would help in the review process.

3. ISSUES REQUIRING FURTHER DISCUSSION

- The Agency asked Gilead to submit the final protocol for Study GS-US-216-0114 to IND 101,283 prior to initiating the study and to include the SAP.
- The Agency informed Gilead that if any proprietary data from other approved drugs is submitted with the NDA, the application will be classified as a 505(b)(2). The Agency advised Gilead to not use the RTV label as a guide for the GS-9350 NDA as RTV does not have an approved indication as a pharmacoenhancer.
- The Agency informed Gilead that PK data in HIV-infected patients will be required for DRV if the DRV PK parameters in the presence of GS-9350 do not match the DRV PK parameters in the presence of RTV in healthy subjects. If the target PK parameters are met, the need for further studies will depend on the results of ongoing and long-term data. Therefore, the Agency informed Gilead that this issue may require further discussion.
- Additional discussion is required regarding the pediatric investigational plans.

4. ACTION ITEMS

- The Agency will provide comments on studies the Phase 3 protocols GS-US-216-0102 and GS-US-236-0103, submitted to IND 103,093
- The Agency will provide recommendations for implementation and conduct of the snapshot methodology for the efficacy primary endpoint
- The Agency will provide comments on the GS-9350 QTc study report.
- The Agency will re-send the comment from IRT regarding the elvitegravir QTc study and suprathereapeutic dose (see below).
- Gilead will submit Proposed Pediatric Study Request for EVG, GS-9350 and FDC tablet
- Gilead will submit the study report for the DRV/GS-9350 drug interaction study
- Gilead will submit copies of any communications between Gilead and EMA regarding pediatric drug development

ATTACHMENTS AND HANDOUTS

As a reference, the following comment was previously sent to Gilead in comment 5 of the June 4, 2007 meeting minutes.

QUESTION POSED BY SPONSOR (December 7, 2006/ SN 090):

Does the Agency agree that the results from the Thorough QTc Study confirm the lack of effect of GS-9137 on the QT/QTc interval, and that no further evaluation is warranted in the phase 3 clinical trials?

IRT QT Response (June 4, 2007):

Yes, if you can provide data that confirm that the drug concentrations achieved in this study are higher than those that can be reasonably expected after administration of the highest therapeutic dose. The suprathereapeutic dose provides only a 60% increase in mean Cmax. There may be intrinsic (e.g., hepatic impairment) or extrinsic (e.g., drug-interactions) factors that increase concentrations higher than 3663 ng/mL that have not been considered. The adequacy of the exposures achieved in this study will be a review issue when more clinical studies have been submitted for review.

Follow-up Elvitegravir QTc Comments:

The results of the thorough QT study indicate that the suprathereapeutic dose of GS-9137 results in a mean increase of 60 % in Cmax. In order to determine whether this increase in Cmax

adequately encompasses the maximum concentrations GS-9137 that may be observed clinically, please provide a table which compares the C_{max} of GS-9137 observed in all the pharmacokinetic and clinical studies conducted so far with the C_{max} observed at the supratherapeutic dose in the QT study.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-101283

GI-1

GILEAD SCIENCES
INC

GS-9350

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04/09/2010